Postoperative Protein Sparing With Epidural Analgesia and Hypocaloric Dextrose

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Objective: We examined the hypothesis that epidural analgesia prevents the increase in amino acid oxidation after elective colorectal surgery in patients receiving hypocaloric infusion of dextrose.

Summary Background Data: Increased oxidative protein loss after surgery may adversely affect postoperative outcome. We have previously shown that effective segmental pain relief by epidural analgesia improves postoperative substrate utilization, resulting in less protein catabolism.

Methods: We randomly allocated 10 patients to receive general anesthesia combined with epidural analgesia using bupivacaine/fentanyl and 10 to receive general anesthesia followed by patient-controlled analgesia with intravenous morphine. All patients received a peripheral 72-hour infusion of dextrose 10% from the day before until the second day after surgery. The dextrose infusion rate was adjusted to provide 50% of the patients' resting energy expenditure. The primary end point was whole-body leucine oxidation as determined by a stable isotope tracer technique (L-[1-^{13}C]leucine).

Results: In the intravenous analgesia group, leucine oxidation increased from 19 ± 4 to 28 ± 6 μmol kg^{-1} h^{-1} after surgery. Epidural analgesia prevented this increase of leucine oxidation (preoperative 21 ± 6 μmol kg^{-1} h^{-1}, postoperative 21 ± 5 μmol kg^{-1} h^{-1}). This difference was statistically significant ($P = 0.01$; analysis of variance for repeated measures).

Conclusion: Perioperative epidural analgesia and hypocaloric dextrose infusion suppress the postoperative increase in amino acid oxidation, thereby saving more than 100 g of lean body mass per day.

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Increased oxidative loss of body protein is characteristic of abdominal surgery[1] and, when coupled with prolonged inadequate oral intake, may adversely affect the postoperative clinical course.[2,3] Intravenous administration of dextrose spares protein after surgery, but impairment of glucose utilization due to insulin resistance[4] necessitates the infusion of iso- or hypercaloric quantities.[5,6] Infusion of smaller, hypocaloric amounts of dextrose, ie, provision of energy at a rate below the patient's actual energy expenditure, does not affect postoperative negative nitrogen balance.[7]

There is recent evidence that pain contributes to the catabolic responses to surgery[8] and that effective segmental pain relief by epidural analgesia facilitates glucose utilization[9] mediated through improved insulin sensitivity.[10] One would, therefore, assume that epidural analgesia diminishes the amount of dextrose required to attenuate protein loss after surgery.

To confirm this assumption, we have investigated the effect of continuously maintained epidural analgesia on postoperative protein catabolism in patients receiving intravenous hypocaloric dextrose 24 hours prior to surgery, the hypothesis being that epidural analgesia prevents the increase in amino acid oxidation after colorectal surgery.

MATERIALS AND METHODS

Patients

We performed a prospective randomized controlled trial set in a university teaching hospital. Between February and December 2001, we approached patients undergoing elective resection of colorectal carcinoma at the Royal Victoria Hospital, Montreal, Canada. We excluded patients who had evidence of metastatic disease, congestive heart failure, hepatic disease, diabetes; those who had a serum albumin less than 35 g/L or had anemia (hemoglobin <100 g/L); and those receiving drugs known to have metabolic effects such as corticosteroids or β-blockers.

Procedures and Clinical Management

One investigator approached and enrolled patients (T.S.). Randomization was performed by the same investigator using a sealed envelope with a computer-generated random allocation. We randomly allocated patients to a group of patients receiving general anesthesia combined with periop-

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erative epidural analgesia or to an intravenous analgesia group receiving general anesthesia followed by patient controlled analgesia (PCA) with intravenous morphine. Both anesthesiologist (T.S.) and surgeon (S.M.) were aware of the individual patient's group assignment.

Patients in both groups received infusion of dextrose 10% through a 16 gauge (G) intravenous cannula inserted into a forearm vein. The dextrose infusion was started on the day before surgery at 12:00 AM and continued until 12:00 AM on the second day after surgery. This regimen was adjusted to provide 50% of the patient's resting energy expenditure (REE) as determined by indirect calorimetry. REE was measured at 11:00 on the day before surgery after overnight fasting and on the first and second postoperative day.

All operations started between 8:30 AM and 10:30 AM and were carried out by the same surgeon (S.M.). General anesthesia included thiopentone, fentanyl, rocuronium, nitrous oxide, and isoflurane and was performed by the same anesthesiologist (T.S.). In the epidural analgesia group, an epidural catheter was inserted before induction of anesthesia between T9 and T11. Bupivacaine 0.5% (15-20 mL) was injected to produce a confirmed bilateral segmental sensory block from T4 to S5. Additional 0.25% bupivacaine (5-10 mL) was injected 1 to 2 hours later. At the end of surgery, epidural bupivacaine 0.1% supplemented with 2 μg/mL fentanyl was administered continuously at a rate of 10-15 mL/h and maintained for at least 48 hours. The segmental sensory level of analgesia was assessed twice a day using a blunted needle and ice, and the infusion adjusted to maintain a bilateral sensory block between T7 and L3. In the intravenous analgesia group, pain relief was achieved by PCA with intravenous morphine. The incremental dose of morphine was 1 to 2 mg, lockout was 8 minutes, and dose duration was 30 seconds. The visual analogue scale (VAS) scores at rest and on movement were assessed every 12 hours after surgery (VAS from 0 = no pain to 10 = worst pain imaginable).

Measurements

Before the operation, we recorded gender, age, weight, and height. Whole body leucine and glucose metabolism measurements were made from 9:00 AM to 12:00 AM on the day before surgery prior to dextrose administration and from 9:00 AM to 12:00 AM on the second postoperative day during dextrose infusion. Plasma kinetics of glucose and leucine, ie, the glucose rate of appearance (R_a), the leucine R_a, leucine oxidation, and nonoxidative leucine disposal, were determined by a primed constant infusion of tracer quantities of L-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose. Blood and expired air samples were collected before the infusion to determine baseline enrichments. Priming doses of $NaH^{13}CO_3$ (1 μmol/kg, po), L-[1-^{13}C]leucine (4 μmol/kg, iv), and [6,6-$^{2}H_2$]glucose (22 μmol/kg, iv) were administered, followed by infusions of L-[1-^{13}C]leucine (0.06 μmol kg^{-1} min^{-1}) and [6,6-$^{2}H_2$]glucose (0.44 μmol kg^{-1} min^{-1}). For the determination of $^{13}CO_2$ isotope enrichments, 4 expired breath samples were taken after 150, 160, 170, and 180 minutes of isotope infusion. In addition, 4 arterialized blood samples were collected to determine whole body leucine and glucose kinetics. Plasma concentrations of glucose, lactate, insulin, glucagon, and cortisol were determined at 180 minutes of the pre- and postoperative isotope infusion periods.

The patient's REE was measured by indirect calorimetry (Datex Instrumentarium Deltatrac, Helsinki, Finland). The subjects were lying in a semirecumbent position (20°) and breathing room air in the ventilated hood for 30 minutes on each occasion. Oxygen consumption and carbon dioxide production were measured. Energy expenditure and respiratory quotient were calculated. Average values were taken, with a coefficient of variation less than 10%. Carbohydrate and lipid oxidation rates were calculated using standard formulas.[11] Protein oxidation was calculated using the measured rate of leucine oxidation and assuming that leucine represents 8% of total body protein.[12]

Analytical Methods

Plasma enrichments of [1-^{13}C]α-KIC were analyzed by electron-impact selected-ion monitoring gas chromatography mass spectrometry (GC/MS) using the method described by Mamer and Montgomery,[13] except that *t*-butyldimethylsilyl derivatives was prepared.[9] Expired $^{13}CO_2$ enrichments were analyzed by isotope ratio-mass spectrometry (IRMS Analytical Precision AP 2003, Manchester, UK).[9] Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-$^{2}H_2$]glucose enrichment was determined by GC/MS using electron-impact ionization.[9] In each analysis run, duplicate injections were always performed, and their means taken to represent enrichment.

Plasma glucose concentrations were determined by a glucose oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate concentrations were measured by an assay based on lactate oxidase using the synchron CX system (Beckman Instruments). Serum concentrations of insulin and plasma concentrations of glucagon and cortisol were determined by radioimmunoassays (Amersham International, Amersham, Bucks, UK).

Calculation of Whole-Body Leucine and Glucose Kinetics

Leucine and glucose kinetics were calculated by conventional isotope dilution methodology using a 2-pool stochastic model during steady-state conditions. If an isotope steady state exists, the R_a of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (APE: atom percentage excess) calculated by: $R_a = F\ (APE_{inf}/APE_{pl} - 1)$, where F is the tracer infusion rate, APE_{inf} and APE_{pl} the tracer enrichments in the infusate and plasma,

respectively. The APE used in this calculation represents the mean of 4 APE determined during steady-state conditions.

The R_a of leucine represents the total movement of leucine into and from the plasma pool. Under steady-state conditions, leucine flux (Q) is defined by the equation: Q = S + O = B + I, where S is the rate at which leucine is incorporated into body protein (nonoxidative leucine disposal), O is the rate of leucine oxidation, 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 and diet. In the postabsorptive state, the sole source of the essential amino acid leucine for protein synthesis and oxidation is that derived from the breakdown of endogenous proteins. Plasma enrichments of [1-^{13}C]α-KIC during L-[1-^{13}C]leucine infusion were used as the basis for the calculation of both flux and oxidation of leucine, because it represents the intracellular precursor pool enrichment more precisely than leucine itself.[14] In the calculation of leucine oxidation, factors of 0.76 for the fasting (preoperative) state and 0.81 for the fed (postoperative) state were applied to account for the incomplete recovery of labeled ^{13}C-carbon dioxide from the bicarbonate pool.[12,15]

Under postabsorptive conditions, the R_a of glucose represents endogenous production of glucose. During glucose infusion, endogenous glucose production was calculated by subtracting the postoperative glucose infusion rate from the total R_a of glucose.

Endpoints, Sample Size Calculation and Statistical Analysis

The primary end point was whole-body leucine oxidation on the second postoperative day. Secondary endpoints included carbohydrate oxidation, the leucine rate of appearance, and nonoxidative leucine disposal after surgery. On the basis of our previous studies,[9,16] an alleviation of the postoperative increase of mean leucine oxidation of at least 20% was defined as clinically relevant. Ten patients per group provided more than 95% power for a F-test to detect this difference at a 5% significance level, assuming an actual SD among the appropriate means within the range of the effect size.

Results are expressed as mean ± SD. Statistical analysis was performed using ANOVA for repeated measures. Differences were judged significant if P was 0.05 or less.

TABLE 1. Characteristics of the Patients*

Characteristic	Intravenous Analgesia Group	Epidural Analgesia Group
Age, y	68 ± 8	64 ± 16
Gender, M/F	6/4	4/6
Weight at admission, kg	68 ± 8	67 ± 7
Height, cm	165 ± 8	166 ± 13
Type of surgery		
Hemicolectomy	4	4
Sigmoid colectomy	6	6
Duration of surgery (min)	198 ± 79	203 ± 79

*Values are mean ± SD.

Ethics and Consent

The study was approved by the Ethics Committee of the Royal Victoria Hospital, Montreal, Canada. The study was done in accordance with the Declaration of Helsinki, and written consent was obtained from patients before enrolment.

RESULTS

Table 1 shows the preoperative demographic profile of the patients studied. No relevant differences were observed between the 2 groups. Mean estimated intraoperative blood loss was 305 ± 142 mL in the epidural analgesia group and 330 ± 326 mL in the intravenous analgesia group. There was no clinical evidence of thrombophlebitis at the infusion site in either group and the perioperative course was uneventful in all patients. The VAS scores at rest and on movement in the epidural analgesia group were lower than in the intravenous analgesia group throughout the study period (Table 2). In the

TABLE 2. Postoperative Pain Visual Analogue Score at Rest and on Movement*

	Intravenous Analgesia Group		Epidural Analgesia Group	
	At Rest	On Movement	At Rest	On Movement
12 h After surgery	2.2 ± 1.1	4.2 ± 0.9	1.2 ± 1.0	2.1 ± 1.1
24 h After surgery	2.2 ± 0.9	4.5 ± 0.7	1.4 ± 1.0	2.4 ± 1.0
36 h After surgery	2.3 ± 0.9	4.1 ± 0.7	1.2 ± 0.7	2.7 ± 0.7
48 h After surgery	2.1 ± 1.0	3.9 ± 0.6	1.3 ± 0.7	2.6 ± 0.7

*Values are mean ± SD.

intravenous analgesia group, the REE was 1432 ± 155 kcal/d before surgery and 1475 ± 220 kcal/d on the first postoperative day. The corresponding REE in the epidural analgesia group were 1393 ± 229 kcal/d and 1520 ± 31 kcal/d. The total amount of dextrose infused in the epidural analgesia group was 560 ± 105 g and 554 ± 65 g in the intravenous analgesia group, equivalent to 719 ± 84 kcal/d. Whole-body oxygen consumption increased 2 days after surgery in patients receiving intravenous analgesia, while it remained unchanged in the epidural analgesia group (Table 3). Whole-body carbon dioxide production did not significantly change 2 days after surgery in either group (Table 3). In the epidural analgesia group, the respiratory quotient and carbohydrate oxidation increased after surgery to a greater extent than in the intravenous analgesia group (Table 3). The postoperative decrease in lipid oxidation was more pronounced in the epidural than in the intravenous analgesia group (Table 3). Hypocaloric dextrose suppressed endogenous glucose production to a similar degree in the 2 study groups (Table 3). The plasma concentrations of glucose, insulin, and cortisol postoperatively increased to the same extent in both groups, while the plasma concentrations of glucagon and lactate did not change significantly (Table 3).

Leucine rate of appearance, an estimate of whole-body protein breakdown, increased from 111 ± 17 μmol kg^{-1} h^{-1} to 137 ± 35 μmol kg^{-1} h^{-1} in the epidural analgesia group and from 107 ± 13 μmol kg^{-1} h^{-1} to 142 ± 34 μmol kg^{-1} h^{-1} in the intravenous analgesia group (Table 4). Nonoxidative leucine disposal, an estimate of whole-body protein synthesis, increased from 90 ± 16 μmol kg^{-1} h^{-1} to 117 ± 33 μmol kg^{-1} h^{-1} in the epidural analgesia group and from 88 ± 12 μmol kg^{-1} h^{-1} to 114 ± 30 μmol kg^{-1} h^{-1} in the intravenous analgesia group (Table 4). In the epidural analgesia group, the leucine oxidation remained at the preoperative level, whereas in the intravenous analgesia group, it increased by almost 50% from 19 ± 4 μmol kg^{-1} h^{-1} to 28 ± 6 μmol kg^{-1} h^{-1} (Table 4).

DISCUSSION

We have shown that the increase in whole-body leucine oxidation after colorectal surgery can be suppressed by perioperative epidural analgesia and hypocaloric dextrose infusion. Assuming that leucine represents 8% of whole-body protein, the daily oxidative protein loss in patients of the intravenous analgesia group was 76 g, an observation in agreement with previous results obtained in similar patients.[7] In the present study, epidural analgesia diminished this wastage to 54 g of protein, thereby saving 22 g of protein, or more than 100 g of muscle mass per day. This extent of protein sparing is greater than that previously achieved with pharmacological and nutritional interventions in patients undergoing elective colorectal surgery. Biosynthetic growth hormone in the presence of intravenous nutrition (7 g N, 500 kcal as carbohydrate and 450 kcal as lipid) preserved 500 g of muscle mass over a period of 7 days.[17] The anticatabolic effect of

TABLE 3. Changes in Various Variables From Baseline*

	Intravenous Analgesia Group (N = 10)			Epidural Analgesia Group (N = 10)			
Variable	At Baseline	2 Days After Surgery	Change	At Baseline	2 Days After Surgery	Change	*P* Value
Oxygen consumption (mL/min)	211 ± 2	228 ± 25	17 ± 19	209 ± 31	204 ± 32	−3 ± 15	0.02
Carbon dioxide production (mL/min)	171 ± 20	187 ± 21	16 ± 16	166 ± 25	172 ± 24	6 ± 11	0.13
Respiratory quotient	0.81 ± 0.02	0.82 ± 0.02	0.01 ± 0.02	0.80 ± 0.02	0.84 ± 0.04	0.04 ± 0.02	0.01
Carbohydrate oxidation (g/d)	121 ± 29	138 ± 28	16 ± 30	103 ± 27	155 ± 39	53 ± 22	0.01
Lipid oxidation (g/d)	80 ± 8	75 ± 14	−6 ± 15	83 ± 20	62 ± 27	−16 ± 22	0.04
Glucose rate of appearance (μmol/kg/min)	13.3 ± 3.2	19.8 ± 2.9	6.6 ± 3.8	13.9 ± 2.0	20.2 ± 5.0	6.3 ± 4.0	0.87
Endogenous glucose rate of appearance (μmol/kg/min)	13.3 ± 3.2	9.4 ± 2.5	−3.9 ± 3.9	13.9 ± 2.0	8.7 ± 4.2	−5.2 ± 3.6	0.44
Glucose (mmol/L)	5.3 ± 0.8	7.8 ± 1.1	2.5 ± 1.3	5.4 ± 0.5	7.7 ± 1.4	2.3 ± 1.4	0.84
Lactate (mmol/L)	1.1 ± 0.2	0.9 ± 0.3	−0.2 ± 0.3	1.0 ± 0.8	0.7 ± 0.2	−0.3 ± 0.5	0.92
Insulin (pmol/L)	72 ± 15	135 ± 41	63 ± 47	62 ± 23	99 ± 47	37 ± 38	0.20
Glucagon (pmol/L)	25 ± 10	24 ± 14	−1 ± 6	32 ± 18	31 ± 28	−1 ± 16	0.96
Cortisol (nmol/L)	224 ± 71	371 ± 123	148 ± 92	226 ± 104	446 ± 170	220 ± 188	0.29

*Plus-minus values are mean ± SD. *P* values are the probability that the changes from pre- to postoperative values were modulated by the type of analgesia that is the interaction term of the analysis of variance between effects for time and type of analgesia.

TABLE 4. Changes in Leucine Kinetics From Baseline*

Variable	Intravenous Analgesia Group (N = 10)			Epidural Analgesia Group (N = 10)			*P* Value
	At Baseline	2 Days After Surgery	Change	At Baseline	2 Days After Surgery	Change	
Leucine rate of appearance (μmol/kg/h)	107 ± 13	142 ± 34	35 ± 31	111 ± 17	137 ± 35	26 ± 22	0.51
Leucine oxidation (μmol/kg/h)	19 ± 4	28 ± 4	9 ± 5	21 ± 6	21 ± 5	0 ± 6	0.01
Nonoxidative leucine disposal (μmol/kg/h)	88 ± 12	114 ± 30	26 ± 27	90 ± 16	117 ± 33	27 ± 21	0.93

*Values are mean ± SD. *P* values are the probability that the changes from pre- to postoperative values were modulated by the type of analgesia that is the interaction term of the analysis of variance between effects for time and type of analgesia.

growth hormone administration was less pronounced in surgical patients receiving hypocaloric dextrose (400 kcal) without amino acids or fat.[18] Postoperative intravenous provision of glutamine peptide with 0.23 g N/kg and 33 kcal/kg per day as carbohydrate and fat, preserved a total of 300 g of muscle mass after 5 days of treatment.[19] Intravenous hypercaloric administration of xylitol or fructose instead of dextrose, supplemented with amino acids (1.3 g/kg per day), decreased postoperative protein loss by 28 g over a period of 5 days.[20]

That epidural analgesia has protein sparing effects in the presence of isocaloric or hypercaloric intravenous nutrition has been shown before in patients undergoing colorectal surgery.[16,21] Epidural administration of bupivacaine preserved 76 g of protein after 5 days of intravenous nutrition consisting of 30 kcal/kg (50% carbohydrates and 50% fat) and 0.18 g N/kg per day.[21] In patients receiving nutrition with 0.1 g/kg N and 20 kcal/kg per day (60% fat, 35% carbohydrate, and 5% protein contribution) started 6 days before the operation epidural analgesia, restricted to the first 24 hours after surgery, reduced the oxidative protein loss by 20 g on the second postoperative day.[16] Hypercaloric intravenous nutrition providing approximately 2400 kcal per day, with 66% of nonprotein kcal as fat and 18 g N maintained total body protein after upper abdominal surgery only in patients receiving epidural analgesia.[22]

Our demonstration that segmentally appropriate epidural analgesia prevents the postoperative increase in oxidative protein loss with half the commonly used energy and without nitrogen intake has a valuable practical application. The fact that isocaloric and hypercaloric intravenous feeding requiring central venous cannulation is associated with hyperglycemia and increased morbidity in well-nourished surgical patients is an impediment to its routine use.[23–25] However, if the nutrient load can be decreased, use can be made of peripheral veins and hyperglycemia can be avoided, thus making this therapy safer and available to more patients.

Modulation of the endocrine responses to surgery might be one causative factor responsible for the protein-sparing action of epidural analgesia.[26] Epidural administration of local anesthetic attenuates the increase in plasma levels of counterregulatory hormones during surgery, thereby improving insulin sensitivity[10] and glucose utilization,[9,27] with positive impact on protein economy.[9,12] Although the postoperative increase in plasma insulin levels was not modified by the type of analgesia, the greater augmentation of carbohydrate oxidation accompanied by a more pronounced decrease in lipid oxidation may indicate a better insulin sensitivity in the epidural analgesia group.[10]

The fact that preoperative fasting was avoided in our protocol also presumably contributed to the anticatabolic effects of epidural analgesia. There is evidence that performing surgery in the fed state, after a 12-hour administration of dextrose infused at a rate greater than in the present study (5 mg kg^{-1} min^{-1}), can normalize postoperative insulin sensitivity[28] and promote nitrogen retention.[29]

The present findings show that combined epidural analgesia and peripheral infusion of hypocaloric dextrose creates a simpler and a metabolically more favorable setting for recovery of patients after colorectal surgery. Whether the prevention of postoperative loss of body protein is beneficial in fit patients with uncomplicated recovery from elective abdominal procedures is still questionable. However, recent evidence does indicate that epidural analgesia is a key component of strategies to enhance functional exercise capacity and quality of life after colorectal surgery.[30,31]

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