A Randomized Controlled Trial of the Anticatabolic Effect of Epidural Analgesia and Hypocaloric Glucose

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Background and Objectives: The goal of the present study was to investigate whether epidural analgesia exerts a protein-sparing effect after colorectal surgery in the presence of hypocaloric glucose supply initiated with surgical skin incision.

Methods: We randomly allocated 10 patients to receive general anesthesia combined with epidural anesthesia with bupivacaine, followed by epidural analgesia using bupivacaine/fentanyl, and 10 patients to receive general anesthesia, followed by patient-controlled analgesia with intravenous morphine. All patients received a 48-hour infusion of glucose 10% from surgical skin incision until the second day after surgery. The glucose infusion rate provided 50% of the patient's resting energy expenditure. Kinetics of protein and glucose metabolism were assessed by a stable-isotope tracer technique (L-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose).

Results: The rate of appearance of leucine increased in the intravenous-analgesia group (112 ± 29 to 130 ± 25 μmol/kg/h) 2 days after surgery, and this increase was more pronounced than in the epidural analgesia group (preoperative 120 ± 24, postoperative 123 ± 22 μmol/kg/h, $P < .05$). Leucine oxidation rate increased in the intravenous analgesia group from 17 ± 8 to 23 ± 8 μmol/kg/h and in the epidural group from 17 ± 6 to 19 ± 7 μmol/kg/h without the difference between the groups reaching statistical significance ($P = .067$). Nonoxidative leucine disposal remained unaltered in both groups. No differences in glucose metabolism were seen between the groups.

Conclusions: Epidural analgesia inhibits the increase in whole-body protein breakdown in patients receiving perioperative hypocaloric glucose infusion initiated with surgical skin incision. However, oxidative protein loss, protein synthesis, and glucose metabolism are not affected by epidural analgesia. *Reg Anesth Pain Med 2007;32: 227-232.*

Key Words: Epidural analgesia, Stable isotopes, Protein metabolism, Glucose.

Pain per se in the absence of surgical tissue trauma stimulates the classic endocrine stress response resulting in hyperglycemia and negative nitrogen balance, typical features of the catabolic response to surgery.[1,2] Furthermore, effective segmental pain relief by epidural anesthesia has been shown to attenuate hyperglycemia and to maintain protein homeostasis in patients undergoing major abdominal surgery.[3-5] We recently demonstrated that intraoperative epidural anesthesia followed by continuous epidural analgesia in contrast to general anesthesia alone combined with postoperative intravenous analgesia by use of morphine prevents the loss of whole-body protein on the second day after colorectal surgery.[6] In this study, all patients received glucose infusions from 24 hours before until 2 days after the operation. The avoidance of prolonged fasting as exercised in that protocol gains metabolic importance because evidence suggests that preoperative administration of glucose improves insulin sensitivity and decreases nitrogen loss after surgery.[7,8] Hence, whether and to what extent early provision of glucose contributed to the protein-sparing effect of epidural analgesia as observed in that protocol remained unclear. The goal of the present study was to investigate whether the anticatabolic effects of epidural analgesia in the presence of energy supply can be also obtained with

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a later, intraoperative start of intravenous glucose. Indicators of protein and glucose catabolism (i.e., protein breakdown, amino acid oxidation, protein synthesis, and glucose production) were assessed by stable isotope tracer kinetics that used [6,6-$^2H_2$]glucose and L-[1-^{13}C]leucine before and after colorectal cancer surgery.

Materials and Methods

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.

Patients

We performed a prospective, randomized, controlled trial set in a university teaching hospital. We approached patients undergoing elective open resection of localized, nonmetastatic 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. Two investigators approached, enrolled, and randomized consenting patients (TS+RL). Patients were randomly allocated to a group of patients receiving general anesthesia combined with perioperative epidural analgesia or to an intravenous-analgesia group receiving general anesthesia, followed by patient-controlled analgesia (PCA) with intravenous morphine. Both anesthesiologist (TS, RL) and surgeon (SM) were aware of the individual patient's group assignment.

Patients in both groups received infusion of glucose 10% through a 16-gauge intravenous cannula inserted into a forearm vein. The glucose infusion started with skin incision and continued until 12:00 noon on the second day after surgery. The infusion rate was adjusted to provide 50% of the patients' resting energy expenditure (REE), as determined by indirect calorimetry at 11:00 a.m. on the day before surgery and on the first and second postoperative days. This hypocaloric rate was chosen because glucose administered at a higher dose in surgical patients is associated with significant hyperglycemia (i.e., blood glucose concentrations $>$10 mmol/L).[5,9]

All operations were carried out by the same surgeon. General anesthesia included propofol, fentanyl (3 to 5 μg/kg), rocuronium, nitrous oxide, and isoflurane and was performed by 1 of 2 anesthesiologists. In the epidural-analgesia group, an epidural catheter was inserted before induction of anesthesia between T9 and T11. Bupivacaine 0.5% (15 to 20 mL) was injected to produce a confirmed bilateral, segmental-sensory block from T4 to L3. Additional 0.25% bupivacaine (5 to 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 to 15 mL/h and maintained for at least 48 hours. The segmental-sensory level of analgesia was assessed twice a day by use of a blunted needle and ice, and the infusion was 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 morphine consumption in the PCA group was not recorded. No supplemental analgesics, such as NSAIDs, were given. The numerical visual analog scale (VAS) scores at rest and on movement were assessed every 12 hours after surgery (0 = no pain; 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 a.m. to 12:00 noon on the day before surgery and from 9:00 a.m. to 12:00 noon on the second postoperative day during glucose infusion. Plasma kinetics of glucose and leucine, that is, 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-$^2H_2$]glucose as described previously.[5,6] Plasma concentrations of glucose, lactate, insulin, glucagon, and cortisol were determined at 180 min of the preoperative and postoperative isotope infusion periods.

The patients' 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%.

Analytical Methods

Plasma enrichments of [1-^{13}C]α-KIC and [6,6-^{2}H2]glucose were analyzed by electron-impact, selected-ion monitoring gas chromatography mass spectrometry (GC/MS) as described earlier.[10] Expired $^{13}CO_2$ enrichments were analyzed by isotope ratio-mass spectrometry (IRMS Analytical Precision AP 2003, Manchester, UK). Plasma glucose concentrations were determined by a glucose oxidase method that utilized a Glucose Analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate concentrations were measured by an assay based on lactate oxidase by use of the Synchron CX System (Beckman Instruments, Fullerton, CA). 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 that utilized a 2-pool stochastic model during steady-state conditions. The principles of this calculation have been described in detail previously.[5,6,11] 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.[11] 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.[12,13] 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 endpoint was whole-body leucine oxidation on the second postoperative day. On the basis of our previous studies,[5,6] 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 an *F* test to detect this difference at a 5% significance level, assuming an actual standard deviation among the appropriate means within the range of the effect size.

Table 1. Characteristics of the Patients*

Characteristic	Intravenous Analgesia Group	Epidural Analgesia Group
Age (y)	66 ± 13	69 ± 13
Gender (M/F)	5/5	7/3
Weight at admission (kg)	71 ± 13	73 ± 9
Height (cm)	168 ± 11	172 ± 9
Type of surgery		
Hemicolectomy	3	2
Sigmoid colectomy	7	8
Duration of surgery (min)	194 ± 74	216 ± 94

*Values are presented as means ± SD.

Results are expressed as mean ± SD. Statistical analyses of dependent variables were performed by use of 2-factorial ANOVA for repeated measures. Significant effects induced by feeding were assumed when *P* values for time dependency were below .05. Influences by the analgesic regimen were accepted as significant when the interaction term of the analysis of variance was below .05.

Results

Table 1 shows the preoperative demographic profile of the patients studied. No relevant differences were observed between the 2 groups. No patient suffered from significant blood loss that required transfusion of red blood cells. Both groups were homogenous with respect to the type of surgery (epidural group: 8 sigmoid colectomy, 2 hemicolectomy; intravenous analgesia group: 7 sigmoid colectomy, 2 hemicolectomy). The numerical analgesia 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).

Leucine rate of appearance, an estimate of whole-body protein breakdown, increased from 120 ± 24 μmol/kg/h to 123 ± 22 μmol/kg/h in the epidural-analgesia group and from 112 ± 29 μmol/kg/h to 130 ± 25 μmol/kg/h in the intravenous-analgesia group (Table 3). This increase was more pronounced in the intravenous-analgesia group than in the epidural group. Leucine oxidation rates increased from 17 ± 6 μmol/kg/h to 19 ± 7 μmol/kg/h in the epidural-analgesia group and from 17 ± 8 μmol/kg/h to 23 ± 8 μmol/kg/h in the intravenous-analgesia group. Although a trend toward a greater increase in amino acid oxidation was seen in patients receiving intravenous analgesia, the interaction term of the analysis of variance (probability that the effect of glucose is greater in 1 distinct group) failed to achieve statistical significance ($P = .067$). The rate of nonoxidative leucine disposal, an

Table 2. Postoperative Pain Numeric Analogue Score*

	Intravenous Analgesia Group		Epidural Analgesia Group	
	At Rest	On Movement	At Rest	On Movement
12 hours after surgery	2.0 ± 1.8	4.8 ± 1.6	0.8 ± 2.9	2.9 ± 1.1
24 hours after surgery	2.2 ± 1.6	4.7 ± 1.5	1.4 ± 1.1	2.8 ± 1.2
36 hours after surgery	2.1 ± 1.4	4.4 ± 1.6	1.2 ± 1.3	3.0 ± 1.1
48 hours after surgery	2.1 ± 1.2	4.5 ± 1.6	1.5 ± 2.6	2.7 ± 0.8

*Values are presented as means ± SD.

estimate of whole-body protein synthesis, did not change significantly in either group. The rate of appearance of glucose increased in both groups and the suppression of endogenous glucose production by exogenous glucose infusion was comparable in the 2 study groups (Table 3). The plasma concentrations of glucose, lactate, cortisol, and insulin increased independent of the type of analgesia, and the plasma concentrations of glucagon decreased in both groups (Table 3).

Whole-body oxygen consumption, whole-body carbon dioxide production, and the respiratory quotient increased 2 days after surgery in both groups to a similar degree (Table 4).

Discussion

We demonstrate that epidural analgesia combined with the administration of hypocaloric glucose delivering 50% of the patient's energy expenditure attenuates protein breakdown on the second day after colorectal surgery. The protein-sparing effects of epidural analgesia are well described in the literature.[14] The majority of studies that demonstrate positive effects of neuraxial block on protein homeostasis were conducted in patients receiving alimentary support.[15-17] Hence, differentiation between the impact of the type of analgesia and changes resulting from nutritional factors was not possible. More recent studies controlled for the patients' feeding status indicate that, under fasting conditions, when energy intake is absent, epidural analgesia has no effect on protein catabolism.[5,18] In the presence of energy supply, however, epidural analgesia maintains protein balance and suppresses the postoperative loss of nitrogen.[5,6,18] Although in the present study, epidural analgesia attenuated the increase in protein breakdown after surgery, it failed to inhibit amino acid oxidation, most likely a consequence of the different timing of glucose administration. Whereas hypocaloric glucose in the previous protocol started 24 hours before surgery,[6] glucose infusion in the present study started with surgical skin incision. One may, therefore, speculate that changing the metabolic setting from an overnight fasted to a fed state accentuates the protein-preserving effect of epidural analgesia. This as-

Table 3. Leucine and Glucose Kinetics and Circulating Concentrations of Metabolites and Hormones*

	Intravenous Analgesia Group		Epidural Analgesia Group		*P* Values		
	Baseline	2 Days After Surgery	Baseline	2 Days After Surgery	Glucose†	Analgesia‡	Interaction§
Leucine rate of appearance (μmol/kg/h)	112 ± 29	130 ± 25	120 ± 24	123 ± 22	.003	.929	.028
Leucine oxidation (μmol/kg/h)	17 ± 8	23 ± 8	17 ± 6	19 ± 7	.001	.470	.067
Nonoxidative leucine disposal (μmol/kg/h)	94 ± 14	107 ± 18	103 ± 20	104 ± 18	.052	.689	.082
Glucose rate of appearance (μmol/kg/min)	11.0 ± 2.7	17.9 ± 3.6	11.2 ± 1.4	17.5 ± 2.1	.0001	.936	.655
Endogenous glucose rate of appearance (μmol/kg/min)	11.0 ± 2.7	8.2 ± 3.8	11.2 ± 1.4	7.0 ± 2.3	.0001	.580	.349
Glucose (mmol/L)	5.3 ± 0.6	7.4 ± 1.0	5.4 ± 0.4	7.5 ± 0.8	.0001	.751	.831
Lactate (mmol/L)	1.1 ± 0.3	1.3 ± 0.4	1.0 ± 0.3	1.1 ± 0.3	.026	.341	.961
Cortisol (nmol/L)	212 ± 72	406 ± 140	243 ± 82	356 ± 100	.0001	.775	.219
Insulin (pmol/L)	56 ± 30	99 ± 50	53 ± 22	95 ± 20	.0001	.818	.974
Glucagon (pmol/L)	17 ± 6	14 ± 4	19 ± 4	16 ± 6	.046	.323	.992

*Values are presented as means ± SD.
†Probability that values are influenced by intravenous glucose.
‡Probability that values are influenced by the type of analgesia.
§Probability that the effect of glucose is greater in 1 distinct group.

Table 4. Gaseous Exchange*

	Intravenous Analgesia Group		Epidural Analgesia Group		*P* Values		
	Baseline	2 Days After Surgery	Baseline	2 Days After Surgery	Glucose†	Analgesia‡	Interaction§
Oxygen consumption (mL/min)	215 ± 44	228 ± 37	221 ± 26	233 ± 38	.002	.809	.570
Carbon dioxide production (mL/min)	168 ± 26	190 ± 26	174 ± 17	189 ± 34	.046	.694	.982
Respiratory quotient	0.79 ± 0.06	0.84 ± 0.05	0.79 ± 0.05	0.81 ± 0.04	.047	.391	.430

*Values are presented as means ± SD.
†Probability that values are influenced by intravenous glucose.
‡Probability that values are influenced by the type of analgesia.
§Probability that the effect of glucose is greater in one distinct group.

sumption is supported by the results of studies that show preoperative overnight treatment with glucose improves insulin sensitivity and thereby promotes nitrogen retention after major surgery.[7,8]

The inhibition of the hyperglycemic response to abdominal surgery by epidural analgesia has also long been recognized.[3] In the present protocol independent of the anesthetic technique, circulating glucose concentrations increased 2 days after surgery, lending support to the conclusion that the suppressive effect of epidural analgesia on glucose metabolism is limited to the intraoperative and immediate postoperative period. We assessed glucose production rates in our study because of a biochemical link between perioperative glucose and protein metabolism. Muscle protein is said to be broken down to provide gluconeogenic amino acids as precursors for de novo glucose synthesis in liver and kidney.[5] In our investigation, no relation between whole-body protein breakdown and endogenous glucose production was observed, that is, the inhibition of protein breakdown in the epidural group was not accompanied by a corresponding decrease in glucose production. This finding has 2 possible explanations. First, whole-body glucose production is, depending on the metabolic state, composed of glycogenolysis and gluconeogenesis. Because the use of [6,6-$^2H_2$]glucose as applied in the present protocol does not allow the differentiation between the 2 pathways, the contribution of gluconeogenesis could not be quantified in our patients. Second, the possibility that more factors than the need for gluconeogenic precursors regulate protein breakdown and gluconeogenesis in the perioperative period cannot be ruled out.

Because the present protocol was not designed to elucidate the underlying mechanisms. we can only speculate about the potential factors responsible for the metabolic effects of epidural analgesia. Stimulation of afferent sensory and sympathetic fibers by tissue trauma and activation of efferent hypothalamopituitary pathways have been considered to be one of the main release mechanisms of the catabolic responses to surgery.[14] Block of these pathways by epidural local anesthetics has been shown to prevent the counterregulatory endocrine stress response and to increase insulin sensitivity and glucose utilization, with possible impact on protein economy.[5,14,19] In our study, no modifying effect of epidural analgesia on circulating cortisol, glucagons, or insulin concentrations was observed. Because insulin sensitivity was not measured, we, however, cannot rule out the possibility that improved insulin sensitivity contributed to the inhibitory effect of epidural analgesia on postoperative protein breakdown.

In summary, epidural analgesia and hypocaloric glucose, initiated with surgical skin incision, inhibit the increase in whole-body protein breakdown without significantly affecting glucose metabolism 2 days after colorectal surgery. An anabolic response, however, cannot be achieved by the infusion of glucose, whether patients received epidural analgesia or not. Whether epidural analgesia can promote protein synthesis and induce a positive protein balance if anabolic substrates (i.e., amino acids) are administered together with glucose remains to be determined.

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References

1. Greisen J, Juhl CB, Grofte T, Vilstrup H, Jensen TS, Schmitz O. Acute pain induces insulin resistance in humans. *Anesthesiology* 2001;95:578-584.
2. Wilmore DW. Catabolic illness: Strategies for enhancing recovery. *N Engl J Med* 1991;325:695-702.
3. Schricker T, Lattermann R, Schreiber M, Geisser W, Georgieff M, Radermacher P. The hyperglycae-

mic response to surgery: Pathophysiology, clinical implications and modification by the anaesthetic technique. *Clin Int Care* 1998;9:118-128.
4. Lattermann R, Schricker T, Wachter U, Goertz A, Georgieff M. Intraoperative epidural blockade prevents the increase in protein breakdown after abdominal surgery. *Acta Anaesthesiol Scand* 2001;45: 1140-1146.
5. Schricker T, Wykes L, Carli F. Epidural blockade improves substrate utilization after surgery. *Am J Physiol Endocrinol Metab* 2000;279:E646-653.
6. Schricker T, Meterissian S, Wykes L, Eberhart L, Lattermann R, Carli F. Postoperative protein sparing with epidural analgesia and hypocaloric dextrose. *Ann Surg* 2004;240:916-921.
7. Ljungqvist O, Thorell A, Gutniak M, Haggmark T, Efendic S. Glucose infusion instead of preoperative fasting reduces postoperative insulin resistance. *J Am Coll Surg* 1994;178:329-336.
8. Crowe PJ, Dennison A, Royle GT. The effect of preoperative glucose loading on postoperative nitrogen metabolism. *Br J Surg* 1984;71:635-637.
9. Lattermann R, Carli F, Wykes L, Schricker T. Perioperative glucose infusion and the catabolic response to surgery: the effect of epidural block. *Anesth Analg* 2003;96:555-562.
10. Schricker T, Wykes L, Eberhart L, Carli F, Meterissian S. Randomized clinical trial of the anabolic effect of hypocaloric parenteral nutrition after abdominal surgery. *Br J Surg* 2005;92:947-953.
11. Matthews DE, Motil KJ, Rohrbaugh DK, Burke JF, Young VR, Bier DM. Measurement of leucine metabolism in man from a primed, continuous infusion of L-[1-3C]leucine. *Am J Physiol* 1980;238:E473-479.
12. Ang B, Wade A, Halliday D, Powell-Tuck J. Insulin reduces leucine oxidation and improves net leucine retention in parenterally fed humans. *Nutrition* 2000; 16:221-225.
13. Carli F, Webster JD, Halliday D. A nitrogen-free hypocaloric diet and recombinant human growth hormone stimulate postoperative protein synthesis: Fasted and fed leucine kinetics in the surgical patient. *Metabolism* 1997;46:796-800.
14. Kehlet H. Modification of responses to surgery by neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia, PA: Lippincott-Raven Publishers, 1998:129-175.
15. Carli F, Webster J, Pearson M, Pearson J, Bartlett S, Bannister P, Halliday D. Protein metabolism after abdominal surgery: Effect of 24-h extradural block with local anaesthetic. *Br J Anaesth* 1991;67:729-734.
16. Vedrinne C, Vedrinne JM, Guiraud M, Patricot MC, Bouletreau P. Nitrogen-sparing effect of epidural administration of local anesthetics in colon surgery. *Anesth Analg* 1989;69:354-359.
17. Carli F, Halliday D. Continuous epidural blockade arrests the postoperative decrease in muscle protein fractional synthetic rate in surgical patients. *Anesthesiology* 1997;86:1033-1040.
18. Schricker T, Wykes L, Eberhart L, Lattermann R, Mazza L, Carli F. The anabolic effect of epidural blockade requires energy and substrate supply. *Anesthesiology* 2002;97:943-951.
19. Uchida I, Asoh T, Shirasaka C, Tsuji H. Effect of epidural analgesia on postoperative insulin resistance as evaluated by insulin clamp technique. *Br J Surg* 1988;75:557-562.