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Parenteral nutrition and protein sparing after surgery: do we need glucose?

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Abstract

Although capable of inducing an anabolic state after surgery, parenteral nutrition, including glucose, leads to hyperglycemia. Even moderate increases in blood glucose are associated with poor surgical outcome. We examined the hypothesis that amino acids, in the absence of glucose supply, spare protein while preventing hyperglycemia. In this prospective study, 14 patients with colonic cancer were randomly assigned to undergo a 6-hour stable isotope infusion study (3 hours of fasting followed by 3-hour infusions of amino acids, Travasol [Baxter, Montreal, Canada] 10% at 0.02 mL · kg^{-1} · min^{-1}, with or without glucose at 4 mg · kg^{-1} · min^{-1}) on the second day after colorectal surgery. Protein breakdown, protein oxidation, protein balance, and glucose production were assessed by stable isotope tracer kinetics using L-[1-^{13}C] leucine and [6,6-$^{2}H_2$]glucose. Circulating concentrations of glucose, cortisol, insulin, and glucagon were determined. The administration of amino acids increased protein balance from −16 ± 4 μmol · kg^{-1} · h^{-1} in the fasted state to 16 ± 3 μmol · kg^{-1} · h^{-1}. Combined infusion of amino acids and glucose increased protein balance from −17 ± 7 to 7 ± 5 μmol · kg^{-1} · h^{-1}. The increase in protein balance during nutrition was comparable in the 2 groups (P = .07). Combined administration of amino acids and glucose decreased endogenous glucose production (P = .001) and stimulated insulin secretion (P = .001) to a greater extent than the administration of amino acids alone. Hyperglycemia (blood glucose, 10.1 ± 1.9 μmol/L) occurred only in the presence of glucose infusion. In summary, excluding glucose from a short-term feeding protocol does not diminish the protein-sparing effect of amino acids and avoids hyperglycemia.

1. Introduction

The immediate period after colorectal surgery is characterized by semistarvation due to anorexia and/or restricted oral food intake for medical reasons. Unless nutrients are provided in amounts sufficient to match the demands of catabolism, rapid net loss of lean tissue ensues. Thus, the primary goal of perioperative nutritional support is to attenuate protein wasting by optimizing nutrient delivery within the constraints of major organ function [1].

Parenteral nutrition, that is, the intravenous provision of anabolic substrates together with energy represents a therapeutic modality to achieve this goal. The metabolic efficacy of intravenous feeding strategies using combined glucose and amino acid infusions is well documented in patients undergoing gastrointestinal surgical procedures [2,3]. Although capable of producing nitrogen retention after abdominal surgery, parenteral nutrition, including the administration of glucose, leads to hyperglycemia [3]. As a result of impaired insulin sensitivity, a typical feature of the endocrine response to surgical tissue trauma [4], exogenous glucose increases the blood glucose concentration even when given in small hypoenergetic amounts [5,6]. Considering the detrimental effects of hyperglycemia on outcome, any disturbance of glucose homeostasis by nutritional interventions gains clinical importance, particularly in the surgical patient population [7,8].

The present study was designed to examine whether amino acids, in the absence of additional energy supply, spare protein while avoiding hyperglycemia as observed during the administration of glucose. We therefore assessed the kinetics of protein and glucose metabolism 2 days after

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colorectal surgery in the fasted state and during a 3-hour infusion of amino acids with or without glucose.

2. Materials and methods

2.1. Patients and ethics

The study was approved by the ethics committee of the Royal Victoria Hospital, Montreal, Quebec, Canada. Informed consent was obtained from 14 patients with localized colorectal carcinoma scheduled for elective trans-abdominal resection. None of the patients had significant cardiac, hepatic, renal, or metabolic disease. No subject had developed recent weight loss or had a plasma albumin concentration of less than 35 g/L.

The patients were randomly allocated to a group receiving intravenous amino acids (n = 7) or a group receiving intravenous amino acids and glucose (n = 7).

2.2. Anesthesia and surgical care

Epidural catheters were inserted in one of the thoracic vertebral levels between T10 and T12 of patients on arrival in the anesthetic room. Bilateral sensory block to ice and pin prick from thoracic dermatome level 6 to lumbar dermatome level 1 was achieved with bupivacaine 0.5% and was maintained during the operation with boluses of bupivacaine 0.25% (approximately 10 mL/h). General anesthesia was induced by propofol and continued with 35% nitrous oxide in oxygen and isoflurane at end-tidal concentrations of 0.3 to 0.4 vol% to achieve tolerance of the endotracheal tube and to prevent awareness. All patients received a bolus of 10 mL/kg normal saline before induction followed by 5 $mL \cdot kg^{-1} \cdot h^{-1}$ during surgery. Blood losses were replaced with Pentaspan (Bristol-Myers Squibb, Montreal, Quebec, Canada). All patients received hypoenergetic nutritional supplementation with glucose from 08:00 AM to 08:00 PM on the first postoperative day (100 mL/h glucose 5% equivalent to approximately 1046 kJ [250 kcal]) followed by the infusion of NaCl 0.9% (100 mL/h).

Sensory blockade from T8 to L3 was maintained postoperatively by a continuous epidural infusion of 0.1% bupivacaine supplemented with 3 μg/mL fentanyl administered at a rate between 8 and 14 mL/h. Pain treatment was adjusted to obtain a numerical analogue score at rest of less than 4 (numerical analogue scale from 0 = no pain to 10 = worst pain imaginable).

2.3. Parenteral nutrition

On the second postoperative day, after a 3-hour period of fasting, patients received a 10% amino acid solution without electrolytes (Travasol, Baxter, Montreal, Canada) either alone or together with crystallized beet sugar (10% dextrose anhydrous, Avebe, Foxhol, Holland) at 4 $mg \cdot kg^{-1} \cdot min^{-1}$ for 3 hours. The rate of amino acid infusion was set at 0.02 $mL \cdot kg^{-1} \cdot min^{-1}$ (equivalent to approximately 2.9 $g \cdot kg^{-1} \cdot day^{-1}$) to achieve plasma amino acid concentrations at least 2-fold above basal level [9]. The composition of Travasol (in micromoles per milliliter), which was verified before each administration, was as follows: proline 35, threonine 34, glycine 217, alanine 207, valine 36, methionine 37, isoleucine 34, leucine 45, tyrosine 2, phenylalanine 35, tryptophan 9, lysine 38, histidine 26, and arginine 57. The dextrose solution was prepared by the local pharmacy under sterile conditions and tested for sterility, stability, and absence of pyrogens before infusion. Beet dextrose was chosen because of its low carbon 13 content and therefore the lack of significant alteration of $^{13}CO_2$ enrichment in expired air [10]. Previous studies showed that the infusion of a solution containing beet dextrose and amino acids does not perturb baseline $^{13}CO_2$ enrichment in humans [11].

2.4. Experimental protocol

Plasma kinetics of leucine and glucose were determined by a primed constant infusion of tracer quantities of L-[1-^{13}C]leucine (99% ^{13}C) and [6,6-$^{2}H_2$]glucose (99% ^{2}H, Cambridge Isotope Laboratories, Cambridge, MA). Sterile solutions of labeled isotopes were prepared in the hospital pharmacy and kept at 4°C until administration. All tests were performed in the fasted state beginning at 08:00 AM on the second postoperative day. A superficial vein in the dorsum of the hand was cannulated and the cannula kept patent with saline 2 $mL \cdot kg^{-1} \cdot h^{-1}$. A second vein in the contralateral arm was cannulated to provide access for the infusion of the stable isotopes. Blood and expired air samples were collected before the infusion to determine baseline enrichments. Priming doses of $NaH^{13}CO_3$ 1 μmol/kg, L-[1-^{13}C]leucine 4 μmol/kg, and [6,6-$^{2}H_2$]glucose 22 μmol/kg were administered and followed immediately by continuous infusions of L-[1-^{13}C]leucine 0.06 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and [6,6-$^{2}H_2$]glucose 0.22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ lasting 6 hours. Toward the end of each 3-hour study period, 4 blood and expired breath samples were collected at 10-minute intervals. Each blood sample was transferred to a heparinized tube, centrifuged at 4°C (3000*g*, 15 minutes), and stored at −70°C. Breath samples were collected in a 2-L latex bag and transferred immediately to 20-mL vacutainers.

2.5. Gaseous exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted and fed states. The subjects were lying in a semi-recumbent position (20°) breathing room air in the ventilated hood, for 20 minutes on each occasion. Oxygen consumption ($V\dot{O}_2$) and carbon dioxide production ($V\dot{C}O_2$) were measured, and the respiratory quotient was calculated. An average value of $V\dot{O}_2$, $V\dot{C}O_2$, and respiratory quotient was taken, with a coefficient of variation of less than 10%.

2.6. Analytical methods

2.6.1. Isotopic enrichments

Plasma [1-^{13}C]α-ketoisocaproate (α-KIC) enrichment was determined by electron impact selected-ion monitoring

Table 1
Characteristics of the patients

	Amino acids	Amino acids and glucose
Sex (n, female-male)	4:3	3:4
Age (y)	63 ± 14	60 ± 22
Weight at admission (kg)	69 ± 13	63 ± 13
Height (cm)	168 ± 8	163 ± 10
Surgery (n)		
Hemicolectomy	4	3
Sigmoid colectomy	3	4
Duration of surgery (min)	218 ± 40	208 ± 96

Values are presented as means ± SD.

gas chromatography-mass spectrometry using the method previously described by Mamer, except that the *t*-butyl-methylsilyl rather than trimethylsilyl derivatives were prepared [12]. Expired $^{13}CO_2$ enrichment was determined by isotope ratio mass spectrometry (Analytical Precision AP 2003, Manchester, UK) [12]. Plasma glucose was derivatized to its pentaacetate compound and the [6,6-$^2H_2$]glucose enrichment determined by gas chromatography-mass spectrometry using electron impact ionization [12]. In each analysis run, duplicate injections were given and their means were taken to represent enrichment.

2.6.2. Plasma metabolites and hormones

Plasma glucose was measured by a glucose oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate assay was based on lactate oxidase and was performed using the Synchron CX 7 system (Beckman Instruments). Circulating concentrations of plasma cortisol, insulin, and glucagon were measured by sensitive and specific double-antibody radioimmunoassays (Amersham International, Amersham, Bucks, UK).

2.7. Calculations

Under isotopic steady-state conditions, the rate of appearance (R_a) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (APE or atom percentage excess) calculated by:

$$R_a = (\mathrm{APE_{inf}}/\mathrm{APE_{pl}} - 1)\mathrm{F}(1) \quad (1)$$

where F is the infusion rate of the labeled tracer (μmol · kg^{-1} · min^{-1}), $\mathrm{APE_{inf}}$ is the tracer enrichment in the infusate, and $\mathrm{APE_{pl}}$ the tracer enrichment in plasma, respectively. The APE used in this calculation is the mean of the 4 APEs determined at each steady state. The accuracy of the enrichments at isotopic plateau was tested by evaluating the scatter of values above their mean, expressed as coefficient of variation. A coefficient of variation of less than 5% was used as a confirmation of a valid plateau.

Under steady-state conditions, leucine flux (Q) is defined by the formula:

$$Q = S + O = B + I, \quad (2)$$

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 and diet. When the subjects are in the postabsorptive state, the leucine intake equals zero and $B = Q$. When amino acids are being infused intravenously, the rate of leucine infusion (I) must be subtracted from the total leucine flux to calculate the rate of endogenous leucine release. The rate of exogenous leucine infusion was calculated as the product of the infusate leucine concentration in micromoles per milliliter and the infusion rate in milliliters per minute. Plasma enrichment of [1-^{13}C]α-KIC during the infusion of L-[1-^{13}C]leucine has been used as the basis for calculating both flux and oxidation of leucine. This steady-state reciprocal pool model is considered to represent the intracellular precursor pool enrichment more precisely than leucine itself [13]. In the calculation of oxidation, a factor of 0.76 was applied in the fasted state to account for the fraction of $^{13}CO_2$ released from leucine but retained within slow turnover rate pools of the body [13]. During

Table 2
Leucine and glucose kinetics

	Amino acids		Amino acids and glucose		*P*		
	Fasted	Fed	Fasted	Fed	Nutrition [a]	Type of nutrition [b]	Interaction [c]
Leucine rate of appearance (μmol · kg^{-1} · h^{-1})	125 ± 11	160 ± 15	112 ± 20	143 ± 19	.0001	.1110	.4606
Endogenous leucine rate of appearance (μmol · kg^{-1} · h^{-1})	125 ± 11	107 ± 16	112 ± 20	98 ± 19	.0001	.2353	.3525
Leucine oxidation (μmol · kg^{-1} · h^{-1})	16 ± 4	37 ± 4	17 ± 7	38 ± 7	.0001	.7476	.8331
Nonoxidative leucine disposal (μmol · kg^{-1} · h^{-1})	109 ± 16	122 ± 16	95 ± 17	106 ± 14	.0002	.0535	.5891
Leucine balance (μmol · kg^{-1} · h^{-1})	−16 ± 4	16 ± 3	−17 ± 7	7 ± 5	.0001	.0361	.0731
Glucose rate of appearance (μmol · kg^{-1} · min^{-1})	12.0 ± 1.6	12.0 ± 1.6	11.3 ± 2.0	26.7 ± 2.1	.0001	.0001	.0001
Endogenous glucose rate of appearance (μmol · kg^{-1} · min^{-1})	12.0 ± 1.6	10.2 ± 1.2	11.3 ± 2.0	4.5 ± 2.1	.0009	.0001	.0011

Values are presented as means ± SD.

[a] Probability that values are influenced by intravenous nutrition whether glucose was administered or not.

[b] Probability that values are influenced by the type of intravenous nutrition.

[c] Probability that the effect of intravenous nutrition is different between the 2 groups.

Table 3
Circulating concentrations of metabolites and hormones

	Amino acids		Amino acids and glucose		*P*		
	Fasted	Fed	Fasted	Fed	Nutrition[a]	Type of nutrition[b]	Interaction[c]
Glucose (mmol/L)	5.7 ± 0.5	6.1 ± 0.4	4.9 ± 0.7	10.1 ± 1.9	.0001	.0019	.0001
Cortisol (nmol/L)	278 ± 101	333 ± 168	246 ± 122	314 ± 167	.3350	.5866	.9212
Insulin (pmol/L)	68 ± 31	126 ± 60	75 ± 22	712 ± 117	.0001	.0001	.0001
Glucagon (pmol/L)	124 ± 77	252 ± 101	97 ± 47	150 ± 49	.0004	.0785	.0717

Values are presented as means ± SD.
[a] Probability that values are influenced by intravenous nutrition whether glucose was administered or not.
[b] Probability that values are influenced by the type of intravenous nutrition.
[c] Probability that the effect of intravenous nutrition is different between the 2 groups.

feeding, the fraction of recovery is higher with reported retention factors of 0.90 or greater [14]. Consistent with the previous work of our group on leucine kinetics in patients receiving parenteral nutrition with amino acids, a factor of 0.92 was used in the present study [3]. Leucine balance was calculated as protein synthesis minus endogenous amino acid release, with positive values indicating anabolism. In the fasted state, the R_a of glucose was equal to the endogenous production of glucose. During glucose infusion, endogenous glucose production was calculated by subtracting the glucose infusion rate from the total R_a of glucose.

2.8. Statistics

All data are presented as means ± SD. Based on an expected difference in leucine balance of 10 μmol · kg^{-1} · min^{-1} between the 2 groups and an SD of 5 μmol · kg^{-1} · min^{-1} in each group, a total of 14 patients provides a power of more than 80% with type I error of 5%. Analyses of dependent variables were performed using 2 factorial analysis of variance for repeated measures. Significant effects induced by parenteral nutrition were assumed when *P* values for time dependency (comparing the fasted and fed states) were less than .05. Influences by the feeding regimen were accepted as significant when the interaction term of the analysis of variance was less than 0.05. All analyses were performed using the general linear model in SPSS 11.0 for Windows (SPSS, Chicago, IL).

3. Results

There were no differences between the 2 groups regarding sex, age, height, and weight of patients as well as duration of surgery (Table 1). Estimated blood loss never exceeded 400 mL, and no patient received a blood transfusion.

In all experiments a plateau in the enrichments of [1-^{13}C] α-KIC, [6,6-$^{2}H_2$]glucose, and expired $^{13}CO_2$ was achieved in the fasted and fed states (coefficient of variation <5%). Mean plasma [1-^{13}C]α-KIC enrichment values were between 3.5% and 3.7% (fasting) and between 2.6% and 2.7% (fed) in the amino acids group. Patients in the amino acids/glucose group showed mean plasma [1-^{13}C]α-KIC enrichment values from 3.8% to 4.0% (fasting) and from 2.9% to 3.1% (fed).

Leucine rate of appearance, leucine oxidation, nonoxidative leucine disposal, leucine balance, and glucose production in the fasted state were similar in the 2 groups (Table 2). Intravenous feeding suppressed the endogenous R_a of leucine to the same extent in both groups, whereas leucine oxidation, nonoxidative leucine disposal, and leucine balance increased independent of the type of parenteral nutrition (Table 2). The combined administration of amino acids and glucose decreased endogenous glucose production to a greater extent than the administration of amino acids alone (Table 2).

Whereas plasma concentrations of glucagon similarly increased in both groups, the increase in blood glucose and

Table 4
Gaseous exchange

	Amino acids		Amino acids and glucose		*P*		
	Fasted	Fed	Fasted	Fed	Nutrition[a]	Type of nutrition[b]	Interaction[c]
Oxygen consumption (mL/min)	236 ± 65	247 ± 37	223 ± 48	231 ± 48	.0122	.2521	.8943
Carbon dioxide production (mL/min)	178 ± 43	198 ± 28	166 ± 33	180 ± 30	.0172	.0958	.8330
Respiratory quotient	0.77 ± 0.09	0.80 ± 0.11	0.75 ± 0.03	0.78 ± 0.05	.0721	.2900	.9633

Values are presented as means ± SD.
[a] Probability that values are influenced by intravenous nutrition whether glucose was administered or not.
[b] Probability that values are influenced by the type of intravenous nutrition.
[c] Probability that the effect of intravenous nutrition is different between the 2 groups.

insulin was more pronounced during the infusion of amino acids and glucose (Table 3). Circulating cortisol concentrations did not change significantly (Table 3).

Oxygen consumption and carbon dioxide production increased independent of the type of nutrition (Table 4). The respiratory quotient did not change significantly in the fed state (Table 4).

4. Discussion

We have shown that, after colorectal surgery, short-term infusion of amino acids establishes an anabolic state independent of the provision of energy. Although glucose supplementation inhibits endogenous glucose production and stimulates insulin secretion to a greater extent than the administration of amino acids alone, it leads to severe hyperglycemia.

Protein economy in surgical patients has traditionally been characterized by measuring nitrogen balance, that is, the difference between nitrogen entering and exiting the body. Although often used as a surrogate marker of whole-body protein breakdown and oxidation, urinary nitrogen excretion cannot distinguish effects on protein synthesis from effects on protein degradation. In addition, postoperative retention of nitrogen within the body and underestimation of nitrogen excretion in urine and other routes (feces, skin, wound) invariably lead to falsely positive nitrogen balances [15,16]. Techniques using amino acids labeled with isotopes of carbon have been applied to assess the dynamics of protein catabolism in surgical patients. Studies using L-[1-^{13}C]leucine demonstrate that the principal biochemical mechanisms responsible for negative protein balance after major surgery are increased amino acid release and oxidation together with an insufficient augmentation or fall in whole-body protein synthesis [17,18]. In the present protocol, both types of parenteral nutrition induced a positive leucine balance indicating anabolism. The protein-sparing effect of amino acids was mediated through a decrease in the endogenous rate of leucine appearance and an increase in nonoxidative leucine disposal supporting the previously held conclusion that establishing an anabolic state after gastrointestinal surgery is a function of both, stemming an accelerated proteolysis and stimulating protein synthesis [19,20].

Historically, maintenance of nitrogen equilibrium after surgery has been seen as a result of protein and energy intake [21]. This assumption is based on the fact that there is a biochemical link between perioperative protein and glucose metabolism [22]. As a consequence of impaired insulin sensitivity together with increased plasma concentrations of counterregulatory hormones (cortisol, glucagon, epinephrine, norepinephrine) and the depletion of glycogen stores (due to preoperative fasting), gluconeogenesis increases postoperatively [23]. Muscle protein is broken down to supply amino acids as precursors for de novo glucose synthesis in the liver. It is conceivable that if the rate of gluconeogenesis from amino acids can be suppressed by exogenous glucose, the amount of nitrogen will be available for reincorporation into protein rather than for excretion as urea. Therefore, the efficiency with which amino acids are directed toward anabolic pathways appears to be related to the concomitant reduction of gluconeogenesis. Although correlations between glucose production and protein breakdown have been reported under fasting conditions [24,25], suppression of gluconeogenesis by exogenous glucose fails to decrease proteolysis during and after surgery [24,26]. Parenteral administration of amino acids with or without glucose has long been recognized to improve perioperative protein economy as assessed by nitrogen balance studies [27]. However, little is known about the specific effects of energy and substrate supply on the kinetics of protein and glucose metabolism in patients undergoing abdominal surgery. The present demonstration of a significantly improved leucine balance with anabolic substrate supply in the absence of energy may represent a novel finding in the context of surgery. This finding, however, is supported by previous observations in volunteers, in which amino acids induced an anabolic state by stimulating whole-body and muscle protein synthesis and decreasing endogenous protein breakdown [28,29]. Recent data obtained in healthy men further suggest that increased availability of amino acids might modulate glucose metabolism. In healthy subjects, the infusion of amino acids at a rate identical to that in the present protocol directly inhibited insulin-stimulated glucose transport into skeletal muscle, thereby reducing whole-body glucose disposal [30,31]. Furthermore, a rise in plasma amino acids in the presence of basal insulin levels enhanced gluconeogenesis sufficiently to cause hyperglycemia [32]. The present results do not support the notion that increased circulating concentrations of amino acids disturb glucose homeostasis after surgery. In agreement with observations made in patients after injury, augmenting the plasma levels of amino acids neither stimulated glucose production nor increased the blood glucose concentration [33,34]. Conversely, glucose supplementation resulted in severe hyperglycemia despite the fact that endogenous glucose production was reduced and insulin secretion was enhanced. Hyperglycemia per se has been shown to exacerbate protein catabolism in critically ill patients and may, therefore, be responsible for the (nonsignificant) blunting of the anabolic response in patients receiving amino acids and glucose [35]. Evidence has mounted showing that even moderate increases in blood glucose are associated with poor surgical outcome [7,8,36,37]. In nondiabetic patients, a 1.1-mmol increase in the mean blood glucose level during major surgery was followed by a 30% greater risk of death and infectious, neurologic, renal, and pulmonary complications [36]. On the other hand, there is evidence that strict maintenance of normoglycemia decreases morbidity and mortality in critically ill surgical patients [38-40].

We acknowledge several limitations of this study. The present findings were obtained using relatively large dose of

amino acids and glucose infused over 3 hours and, thus, may not be applicable to surgical patients receiving parenteral nutrition at a lower rate but over a longer period. It also has to be noted that changes detected by isotope infusion studies performed over a few hours after surgery are not necessarily representative of the metabolic alterations during the whole postoperative period.

No attempts were made in our protocol to increase the L-[1-^{13}C]leucine infusion during the administration of Travasol and, therefore, to maintain a constant plasma tracer-to-tracee ratio. Because the calculation of the endogenous rate of leucine appearance is based on the dilution of plasma, which is artificially increased by the infusion of unlabeled leucine, the total rate of leucine appearance and, thus, protein synthesis may have been overestimated [41]. Although, for comparison purpose our results remain valid, they carry an uncertainty of the absolute values of protein kinetics with nutrition.

In conclusion, the presence of glucose as part of a short-term feeding protocol after colorectal surgery does not augment the protein-sparing effect of amino acids but results in hyperglycemia. Whether the prevention of hyperglycemia is beneficial in fit patients with uncomplicated recovery from elective abdominal procedures remains questionable. However, given the potential harm of even moderately increased blood glucose concentrations in surgical patients, our findings may challenge the rationale for using glucose as part of parenteral feeding solutions.

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