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メタデータ	言語: jpn 出版者: 公開日: 2019-06-17 キーワード (Ja): キーワード (En): 作成者: 金森, 理絵 メールアドレス: 所属:
URL	https://doi.org/10.20780/00032174

Hypoglycemia in Laparoscopic Colectomy with Remifentanyl Use and Preoperative Intravenous Glucose Infusion: A Prospective, Randomized, Single-Blind, Controlled Trial

Rie Kanamori, Rika Aihara, Nobutada Morioka* and Makoto Ozaki

Department of Anesthesiology, Tokyo Women's Medical University, Japan

*Corresponding author: Nobutada Morioka, Department of Anesthesiology, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan, Tel: +81-(0)3-3353-8112; Fax: +81-(0)3-3359-2517; E-mail: nobutadamorioka@gmail.com

Received date: Dec 25, 2015; Accepted date: Mar 16, 2016; Published date: Mar 16, 2016

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Abstract

Background: The profound effect of a minimally-invasive procedure under general anesthesia with remifentanyl contributes to suppression of hyperglycemic responses, which was formerly observed as a stress response. However, intraoperative occurrence of hypoglycemia is considered more of a concern. In addition, depending on preoperative nutritional status, critical hypoglycemia may occur during surgery. There are few reports on perioperative glucose metabolism in patients not receiving glucose infusion under anesthesia with remifentanyl. The preoperative fasting period is longer in Japan and preoperative carbohydrate infusion or other pretreatment is not actively performed; thus, the preoperative nutritional status is close to that of starvation. Furthermore, the regulation of glucose metabolism under intraoperative management with potent opioids, such as remifentanyl, as well as the fluctuations in metabolism due to perioperative glucose infusion, is important from the viewpoint of nutritional management.

Objective: This study aimed to examine the impact of preoperative intravenous glucose infusion on glucose, lipid, and protein metabolism before and after surgery under general anesthesia with remifentanyl.

Methods: Forty patients who were scheduled for elective laparoscopic colectomy were randomly assigned to 2 groups: a glucose group that received 1500 mL of a maintenance solution with 10% glucose (glucose 150 g) and a non-glucose group that received the same amount of an extracellular solution without glucose. Glucose metabolism during and after surgery (blood glucose levels, insulin, C-peptide), lipid metabolism (ketone body fractions, free fatty acids), and protein metabolism (urinary 3-methylhistidine) were also evaluated.

Results: No changes were found in background in either group. Blood glucose levels during surgery remained significantly lower ($P=0.003$) in the control group than in the glucose group. One patient had a blood glucose level below 40 mg/dL, and 6 patients had blood glucose levels below 60 mg/dL. Lipid catabolism increased before the induction of anesthesia.

Conclusion: The incidence of hypoglycemia and the rate of lipid catabolism would increase before the induction of anesthesia and during surgery in elective laparoscopic colectomy using remifentanyl without glucose infusion.

Keywords: Remifentanyl; Carbohydrate metabolism; Laparoscopic surgery

Background

Stress induced by surgical procedures causes increased catabolism, which in turn triggers a cascade of enhanced glycogen breakdown, gluconeogenesis, and catabolism of lipids and proteins that eventually leads to increased insulin resistance and postoperative hyperglycemia [1,2]. Persistent postoperative hyperglycemia is a risk factor for infection and various other complications [3].

The Enhanced Recovery After Surgery (ERAS) program, which has been developed mostly in northern-European countries, recommends a preoperative intake of 12.5% carbohydrate-rich drinks (800 mL the night before surgery and another 400 mL up to 2 hours before surgery) to improve postoperative insulin resistance (150 g) [4,5]. However,

studies claiming that preoperative carbohydrate administration reduces postoperative insulin resistance are based on case evaluations of a small number of patients [6-8]. Other studies have shown that postoperative insulin resistance is not affected even with a preoperative carbohydrate load [9,10-12]. The effects of preoperative carbohydrate administration on metabolism during surgery are also unclear. In addition, few studies exist regarding the effects of preoperative intravenous carbohydrate administration in Japanese patients. Recent controversial issues are discussed, such as insulin resistance resulting from various factors, such as surgical invasion, and the associated hyperglycemia. Laparoscopic surgery, which is a minimally invasive procedure, is presently widely performed to reduce surgical invasion. The use of short-acting opioids, such as remifentanyl, enables maintenance of adequate blood opioid concentrations during surgery, contributing to further reduction in surgical invasion. In this situation, a new need for glucose infusion presented itself. Unlike the world standard for preoperative treatment, mechanical preoperative

treatment and extended fasting continue to be strictly performed in Japan. Additionally, fluctuations in intraoperative blood glucose levels at present differ from those in the past due to anesthetic management geared toward minimizing surgical invasion; however, no studies regarding this had been conducted. Therefore, in our study we administered 150 g of intravenous glucose to patients undergoing elective laparoscopic colectomy during the period between the night before surgery and the start of surgery. We then examined fluctuations in intraoperative blood glucose levels and specifically the impact on glucose metabolism, in addition to lipid and protein metabolism.

Methods

Trial design

This randomized, non-blinded, controlled trial was approved by the Institutional Review Board of Tokyo Women's Medical University and conducted in compliance with the Helsinki Declaration. The patients were fully informed both orally and in writing, and written informed consent was obtained.

Participants

Inclusion criteria: Patients were included if they were 20 years or older; scheduled for elective, morning laparoscopic colectomy in the Department of Gastroenterological Surgery at Tokyo Women's Medical University; and classified as American Society of Anesthesiologists physical status I or II.

Exclusion criteria: Patients were excluded if they had diabetes mellitus or glucose intolerance, severe heart dysfunction, severe renal dysfunction, or severe hepatic dysfunction. Patients were also excluded if they were regarded as inappropriate for the study by the study investigators. The registration period was 2 consecutive years.

Intervention

After informed consent was obtained, each patient's eligibility was assessed. The patients were then randomly assigned to 2 groups: a glucose group and a control group. The patients were randomized by computerized assignment for each group. In the glucose group, the patients were not allowed to eat or drink beginning at 9:00 PM the night before surgery. At that time, they received 1500 mL (glucose 150 g) of a 10% glucose maintenance solution (Physio 35, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which was continued until before induction of anesthesia. Patients in the control group were also not allowed to eat or drink beginning starting at 9:00 PM the night before surgery. They received 1500 mL of an acetate Ringer's solution without glucose (Solyugen F, Nipro Corporation, Osaka, Japan) until the induction of anesthesia.

Outcomes and measurements

The primary endpoints were pre and intraoperative blood glucose levels. Glucose metabolism, lipid metabolism, protein metabolism, and surgical stress were also measured. Glucose metabolism was determined by measuring blood glucose levels, insulin, and C-peptide in blood samples taken before the start of the infusion the night before surgery, before induction of anesthesia the day of surgery, 2 hours after induction of anesthesia, at the end of surgery, and in the early morning the day after surgery. Lipid metabolism was determined by measuring

ketone body fractions and free fatty acids before induction of anesthesia the day of surgery, 2 hours after induction of anesthesia, and at the end of surgery. Protein metabolism was determined by measuring urinary 3-methylhistidine [13-17] from the urine that accumulated between induction of anesthesia and the end of surgery. In addition, surgical stress was determined by measuring catecholamines (epinephrine, norepinephrine, and dopamine) and cortisol in blood samples taken before the induction of anesthesia the day of surgery, 2 hours after the induction of anesthesia, and at the end of surgery.

Treatment

During and after surgery, patients were treated as follows. Before the induction of anesthesia, a thoracic epidural catheter was placed. Anesthesia was induced with 1 mg/kg of propofol, 0.5 µg/kg/min of remifentanyl, and 0.6 mg/kg of rocuronium; anesthesia was maintained with 0.25 to 0.5 µg/kg/min and 1.5% of sevoflurane with 0.25 to 0.5 µg/kg/min of remifentanyl. During surgery, a Ringer's solution without glucose was administered at a rate of 8 to 15 mL/kg/hr. Blood glucose levels during surgery were measured every hour with the simplified method. Insulin was administered if a patient's blood glucose levels were 200 mg/dL or higher, and glucose was administered if blood glucose levels were 40 mg/dL or lower. At the end of surgery, patients were given a bolus of 5 to 8 mL of 0.25% popscaine, and continuous administration was begun at a rate of 4 mL/hr. Patient-controlled analgesia (PCA) was used for pain control. An epidural PCA device was inserted, and the patients were transferred to their rooms. For 24 hours after surgery, 2500 mL of Ringer's solution without glucose was administered. During the study period, intravenous solutions containing carbohydrates, hetastarch, or amino acids were not administered. Patients who received insulin because of high blood glucose levels (≥ 200 mg/dL), patients who received glucose because of low blood glucose levels (≤ 40 mg/dL), patients who received blood transfusions, and patients who were found not to meet the inclusion criteria were withdrawn from the study immediately after they were disqualified.

Statistical analyses

Data were analyzed for all patients who were not withdrawn from the study. A paired t test was used for paired continuous data, and a student's t test was used for unpaired continuous data. A chi-squared test was used for categorical data. All analyses were performed with two-tailed tests. Significance was considered at $P < 0.05$. The mean \pm standard deviation was used to express the variability of data. JMP® (SAS Institute Japan, Ltd., Tokyo, Japan) was used for statistical analyses.

Results

Between April 2010 and March 2012, 40 patients were enrolled in the study; 20 patients each were assigned to the glucose and control groups. Two patients were withdrawn and excluded from the data analysis: one patient whose glucose tolerance met the exclusion criteria and one patient who received glucose because of blood glucose levels ≤ 40 mg/dL. However, analysis also included intraoperative measurements of blood glucose at each measurement point up to the administration of salvage therapy. No differences were found in the patient or surgical characteristics of the groups (Table 1).

	Glucose group n=19	Control group n=19	P value
Men/Women	13/6	11/8	0.35 ^b
Age, mean ± SD, yrs	64 ± 12	61 ± 13	0.50 ^a
Height, mean ± SD, cm	162 ± 8	168 ± 8	0.48 ^a
Body weight, mean ± SD, kg	58 ± 11	59 ± 10	0.80 ^a
ASA Classification, I/II	8/11	6/13	0.32 ^b
Colon/Rectum	12/7	11/8	0.64 ^b
Anesthesia time, mean ± SD, min	252 ± 45	242 ± 35	0.42 ^a
Surgical time, mean ± SD, min	178 ± 43	170 ± 35	0.53 ^a
Amount of solution infused during surgery, mean ± SD, mL	2179 ± 430	2104 ± 523	0.63 ^a
Amount of bleeding during surgery, mean ± SD, mL	20 ± 22	26 ± 42	0.57 ^a
Urinary output during surgery, mean ± SD, mL	559 ± 396	548 ± 546	0.95 ^a

Table 1: Characteristics of the patients and surgical procedures.

Data for glucose metabolism, lipid metabolism, protein metabolism, and surgical stress were analyzed. Blood glucose as the primary endpoints and insulin levels remained significantly higher in the glucose group than in the control group from the induction of anesthesia to the day after surgery ($P < 0.05$ for both parameters, Figure 1). Insulin levels remained significantly higher in the glucose group than in the control group from the induction of anesthesia to end of surgery ($P < 0.00001$) (Figure 1). Ketone body fractions remained

higher in the control group than in the glucose group from the induction of anesthesia to end of surgery ($P < 0.0001$ Table 2). Free fatty acid levels were significantly higher in the control group than in the glucose group at induction of anesthesia ($P = 0.00028$, Table 3). Urinary 3-methylhistidine levels were not statistically significant (0.19 ± 0.19 micromol/day, glucose group; 0.25 ± 0.30 micromol/day), control group, $P = 0.51$).

	Reference range	Group	At induction of anesthesia	2 hrs after induction of anesthesia	At the end of surgery
Total ketone bodies $\mu\text{mol/L}$	Below 130	Glucose group	231 ± 306 ^a	825 ± 503 ^{ab}	882 ± 587 ^{ab}
		Control group	2033 ± 1482	1979 ± 1206 ^b	2728 ± 1784 ^b
Acetoacetic acid $\mu\text{mol/L}$	Below 55	Glucose group	72 ± 84 ^a	214 ± 112 ^{ab}	242 ± 168 ^{ab}
		Control group	495 ± 308	544 ± 236 ^b	611 ± 294 ^b
3-hydroxy butyric acid $\mu\text{mol/L}$	Below 85	Glucose group	163 ± 222 ^a	610 ± 394 ^{ab}	640 ± 434 ^{ab}
		Control group	1661 ± 1160	1729 ± 1172 ^b	2107 ± 1513 ^b
Free fatty acids mEq/L	140-850	Glucose group	516 ± 332 ^a	830 ± 214 ^b	702 ± 198 ^b
		Control group	1199 ± 634	670 ± 233 ^b	754 ± 210 ^b

Data are expressed as mean ± SD; aP < 0.05 (comparison of means between the groups using the Student's t test); bP < 0.05 (comparison of means between the groups using the Student's t test).

Table 2: Time course of parameters used to determine lipid metabolism.

Levels of the stress hormone cortisol were significantly lower ($P = 0.038$) in the glucose group than in the control group 2 hours after induction of anesthesia. Dopamine levels were significantly higher ($P = 0.053$) in the glucose group than in the control group the day after surgery. However, the values were both within the reference ranges (Table 3).

Discussion

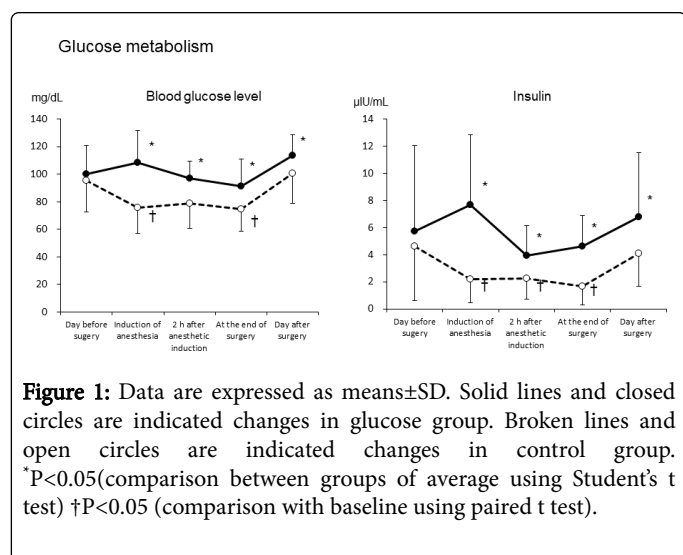
The impact of preoperative glucose infusion on intraoperative blood glucose levels was examined in patients undergoing elective laparoscopic colectomy under general anesthesia using remifentanyl. Neither group had increased blood glucose levels the day after surgery. Therefore, we do not believe postoperative glucose level to be increased

after elective laparoscopic colectomy nor does administering preoperative intravenous glucose (150 g) affect postoperative carbohydrate metabolism.

	Group	At induction of anesthesia	2 hrs after induction of anesthesia	At the end of surgery	Day after surgery
Adrenaline pg/mL	Glucose group	44 ± 34	14 ± 9	54 ± 83	26 ± 13
	Control group	53 ± 57	28 ± 39	69 ± 115	62 ± 103
Noradrenaline pg/mL	Glucose group	236 ± 147	199 ± 85	159 ± 98	236 ± 156
	Control group	220 ± 150	168 ± 67	130 ± 66	200 ± 112
Dopamine pg/mL	Glucose group	11 ± 6	16 ± 6	19 ± 31	24 ± 24 ^a
	Control group	10 ± 8	15 ± 7	7 ± 7	7 ± 5
Cortisol µg/dL	Glucose group	13 ± 5	5 ± 2 ^a	6 ± 6	15 ± 6
	Control group	14 ± 6	7 ± 3	5 ± 2	13 ± 6

Data are expressed as mean ± SD; aP < 0.05 (comparison of means between the groups [Student's t test])

Table 3: Time course of stress hormone levels.



Studies of patients undergoing cholecystectomy, hip arthroplasty, and colorectal surgery have shown that preoperative carbohydrate load reduced postoperative insulin resistance [6-8]. However, in other studies of patients undergoing cardiovascular surgery preoperative glucose administration did not reduce postoperative insulin resistance [9,10] suggesting that the effects differ with varying degrees of surgical stress. Laparoscopic colectomy, the procedure used in our study, causes less surgical stress than does open surgery. In addition, our patients had been given an enough amount of opioids during surgery because

of the use of remifentanyl, and postoperative pain was properly managed with epidural anesthesia, which suppressed the secretion of catecholamines and cortisol [18-20]. All of these factors were thought to have contributed to the fact that postoperative insulin resistance did not increase in our patients.

No changes were seen in blood glucose levels in the glucose group throughout the study period. However, the blood glucose level in the control group was 95.5 ± 22.8 mg/dL the day before surgery and decreased significantly to 75.8 ± 18.6 mg/dL (P=0.005). During surgery, one patient who had a blood glucose level below 40 mg/dL received glucose; 6 patients had blood glucose levels below 60 mg/dL. These episodes of hypoglycemia did not cause clinical symptoms and would have been overlooked had the blood glucose levels not been measured. None of the patients had diabetes mellitus or glucose tolerance before surgery. In Japan, patients who undergo colon surgery are required to fast and mechanical preparation, so their nutritional state is compromised, and they can easily develop hypoglycemia unless glucose is administered before surgery.

Ketone body fractions and free fatty acid levels (parameters for lipid metabolism) were significantly higher before the induction of anesthesia in the control group (P<0.001 for both parameters) and much higher than the upper limit of the reference range, which indicates that lipid is being metabolized due to a lack of glucose. Ketone body fractions increased significantly in both groups until end of surgery because glucose was not administered during surgery. To suppress catabolism, not only preoperative but also intraoperative glucose administration should be considered [21-24].

No difference was found in the levels of urinary 3-methylhistidine, a parameter for protein metabolism, and the values in both groups were within the reference range. Measurements were based on urine samples accumulated between the induction of anesthesia and end of surgery. If protein catabolism started toward the end of the surgical procedure, urinary 3-methylhistidine may have been diluted in a larger amount of accumulated urine, resulting in lower values than the actual values. Also, the time lag for 3-methylhistidine to be excreted in the urine needs to be considered. In evaluating protein catabolism during surgery by using urinary 3-methylhistidine, we believe that more precise results could have been obtained if fresh urine samples obtained at predetermined sampling points, including postoperatively, had been analyzed. In addition, the procedures we studied were relatively short, lasting approximately 3 hours. The time course of blood glucose levels and the degree of lipid breakdown in our patients indicated that protein catabolism might have occurred if the surgical procedures had been longer. While pre- and intraoperative infusion of glucose/carbohydrate has been strongly advocated to prevent postoperative insulin resistance, etc., this study revealed the importance of preoperative infusion of glucose/carbohydrate for prevention of hypoglycemia. In addition, due to advances in minimally invasive techniques typified by the intraoperative use of remifentanyl, there has been no further occurrence of intraoperative hyperglycemia as formerly observed. On the contrary, if a patient remains in a starvation-like state from the preoperative period, intraoperative occurrence of hypoglycemia, etc., is more likely to become an issue. Intraoperative measurement of blood glucose levels is necessary and the simple pre- and/or intraoperative infusion of glucose may be a simple and important protocol in the prevention of critical hypoglycemia.

Conclusions

In elective laparoscopic colectomy, preoperative glucose infusion does not induce intra- or postoperative hyperglycemia. However, gastrointestinal pretreatment results in the diminished nutritional status of patients. Unless glucose infusion is performed in the period between the night before surgery and the start of surgery, blood glucose levels will begin to decrease prior to surgery and lipid catabolism will be enhanced. Furthermore, if glucose is not infused during surgery, lipid catabolism may be further enhanced, thereby inducing critical hypoglycemia. In laparoscopic colectomy requiring gastrointestinal pretreatment, perioperative glucose infusion should be considered for the purposes of preventing hypoglycemia and suppressing catabolism.

Acknowledgement

Dr. Kanamori and Dr. Morioka, who are independent of the commercial funder, had full access to all the data and takes responsibility for the integrity of the data and analyses.

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