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What is the optimal dose of glucose administration during minor surgery under sevoflurane anesthesia?

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Abstract

Purpose. We attempted to identify the optimal infusion rate of glucose to maintain an appropriate usage of energy sources during minor surgery after an overnight fast.

Methods. Forty patients scheduled for tympanoplasty or skin grafting under sevoflurane anesthesia were assigned to four groups. The patients received a 2-h infusion of either saline or glucose at a rate of 0.1, 0.2, or 0.3 $g \cdot kg^{-1} \cdot h^{-1}$. Blood samples were collected before the induction of anesthesia, and at 1 and 2 h after the start of the saline or glucose infusion. Plasma glucose, free fatty acid, β-hydroxybutyrate, acetoacetate, and immunoreactive insulin were measured.

Results. Plasma glucose concentration increased dose-dependently. Immunoreactive insulin levels increased in the groups receiving 0.2 or 0.3 $g \cdot kg^{-1} \cdot h^{-1}$ of glucose infusion. Free fatty acid and ketone bodies did not increase in any glucose infusion groups. The arterial ketone body ratio increased to over 1.00 in the groups receiving 0.2 or 0.3 $g \cdot kg^{-1} \cdot h^{-1}$ of glucose infusion. Glycorrhea was observed only in the group receiving 0.3 $g \cdot kg^{-1} \cdot h^{-1}$ of glucose.

Conclusion. The smaller doses of glucose (0.1–0.2 $g \cdot kg^{-1} \cdot h^{-1}$) prevented lipolysis and hyperglycemia during minor surgery.

Key words: Glucose tolerance, Hyperglycemia, Ketogenesis, Lipolysis

Introduction

We commonly prohibit surgical patients from oral food and water intake for several hours before undergoing anesthesia. When a patient fasts, the store of carbohydrates is decreased, and utilization of fat and protein as energy sources is increased in the body. Therefore, shortening of the preoperative fasting period is necessary. However, adequate oral energy supplementation is often impossible for patients undergoing digestive tract surgery or those scheduled for elective surgery starting early in the morning. Accordingly, it is thought to be reasonable to administer a glucose solution to patients before [1] and during anesthesia to replenish the fuel level [2].

There have been several arguments against conventional glucose administration. Excessive carbon dioxide production may occur due to the rapid degradation of glucose [3]. Hypoglycemia may develop in the fetus when glucose is given to a pregnant woman [4]. The development of intracellular lactic acidosis is likely [5,6]. Cellular injury may be worsened if the patient develops brain ischemia due to anesthetic events or surgical procedures [7].

In the reports cited above, the patients or animals received large amounts of glucose; it is likely that an excessive amount of glucose would produce undesirable effects under severe surgical stress. In patients undergoing major surgery or who are critically ill, several investigators have suggested that the use of smaller doses of glucose could prevent unexpected harmful effects [2,8]. In contrast, appropriate energy support for patients undergoing minor surgery has not been well elucidated. Therefore, in the present study, we attempted to identify the optimal glucose infusion rate to maintain appropriate usage of energy sources in healthy adult patients during minor surgery under sevoflurane anesthesia.

Materials and methods

The study was approved by the Committee for Ethics in Human Research at our institution. Forty adult patients who were scheduled for tympanoplasty or skin grafting of a small area were enrolled. Each patient was classified as American Society of Anesthesiologists physical status 1 or 2. Patients who showed evidence of disorders of metabolism or endocrinology, including diabetes

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mellitus or excessive obesity, or abnormal hepatic or renal function preoperatively were excluded from the study. We explained the details of the study and obtained informed consent from each patient.

To regulate the duration of fasting before surgery, the patients were requested to take no water or food after 9:00 p.m. the night before surgery. The patients were transported to the operating room without any medication at 7:00 a.m. to prepare for the surgical procedures starting at 9:00 a.m. A polytetrafluoroethylene catheter was inserted into a cubital vein under local anesthesia, and a 0.9% NaCl solution was infused at a rate of $5\,ml \cdot kg^{-1} \cdot h^{-1}$. Blood pressure was recorded by the oscillometric method and heart rate by standard lead II electrocardiography with a computerized monitoring system (Patient Monitor Solar 7000, Marquette Electronics, Milwaukee, WI, USA) at 3-min intervals. The pulse oximeter value was also observed on the same monitoring system via a sensor contacting the left index finger. A 22 G polytetrafluoroethylene catheter was inserted into a radial artery under local anesthesia for the collection of blood samples. A urinary catheter was also placed in the urinary bladder under local anesthesia for urine samples.

The trachea was intubated following the administration of $5\,mg \cdot kg^{-1}$ of thiamylal and $0.1\,mg \cdot kg^{-1}$ of vecuronium bromide at 8:15 a.m. No additional muscle relaxant was given during surgery. Anesthesia was maintained by inhalation of a gas mixture of nitrous oxide (66%), sevoflurane, and oxygen (33%). The sevoflurane concentration was adjusted by the anesthesiologist to maintain the mean arterial blood pressure within 20% of the baseline. No adjunct anesthetics or vasoactive drugs were administered. The lungs were ventilated mechanically with a tidal volume of 8–$10\,ml \cdot kg^{-1}$, and the ventilatory rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 35–40 mmHg. The end-tidal carbon dioxide partial pressure was continuously analyzed by the computerized monitoring system described above.

The 40 patients were randomly assigned to four groups. Patients in group 1 additionally received saline at a rate of $0.5\,ml \cdot kg^{-1} \cdot h^{-1}$ for 2 h during surgery. Patients in groups 2, 3, and 4 were additionally infused with a 20% glucose solution at a rate of 0.1, 0.2, or $0.3\,g \cdot kg^{-1} \cdot h^{-1}$ for 2 h, respectively, using an electrically driven syringe pump (Type STS-535, Terumo, Tokyo, Japan).

For intraoperative determination of blood loss, the sponges were weighed. If the blood loss was over 200 g within 2 h after the start of surgery, the patient was excluded from the study.

Blood samples were collected 20 min before the induction of anesthesia and 1 and 2 h after the start of glucose infusion. Anesthesia was maintained for at least 120 min after the start of glucose infusion, even if the surgery was completed earlier than anticipated. If the duration of surgery was less than 100 min, the patient was excluded from the study. Urine samples were also taken 20 min before the induction of anesthesia and 2 h after the start of glucose administration. Following completion of the surgical procedure, anesthetic administration was discontinued. After the patient opened his or her eyes and took a deep breath in response to a verbal command, the endotracheal tube was removed. Plasma was separated from whole blood by centrifugation and stored at $-20°C$ until analysis. The plasma glucose concentration was analyzed immediately after centrifugation. The plasma glucose concentration was determined by the glucose-oxidase method (Glucose B-test Wako, Wako Pharmaceutical, Osaka, Japan); free fatty acid (FFA) was assayed by the acyl-CoA oxidase method (NEFA C-test Wako, Wako), β-hydroxybutyrate (β-HB) and acetoacetate (AA) by Williamson's enzyme methods (Ketone-H, Ketone-A, Cerotec, Sapporo, Japan), and immunoreactive insulin (IRI) by radioimmunoassay. The arterial ketone body ratio (AKBR), which was reported to reflect the reduction-oxidation level of mitochondria in the liver cells, was calculated based on obtained plasma β-HB and AA values according to the method described by Ozawa and his colleagues [9].

Values are expressed as means ± SD. For the patients' background data, the differences in nominal variables among the groups were assessed by chi-square tests, and the differences in numerical variables were tested by one-way factorial analysis of variance (ANOVA). Two-way repeated-measures ANOVA was performed to evaluate differences among and across the groups. Intergroup differences at each time point were compared by one-way factorial ANOVA followed by Student-Newman-Keuls multiple comparisons. Intragroup differences were tested by one-way repeated-measures ANOVA followed by mean comparison contrast analysis. Calculations were made by Super ANOVA (Abacus Concepts, Berkeley, CA, USA). P values less than 0.05 were considered statistically significant.

Results

Patient background data are shown in Table 1. There were no significant differences among the four groups. The blood samples taken 20 min before the induction of anesthesia did not reveal any significant differences in glucose concentrations among the groups.

The data obtained from the analysis of plasma are given in Table 2. Plasma glucose concentrations were significantly elevated after the start of saline or glucose

Table 1. Background data of the subjects, surgical procedure, and water balance

Parameter	Group 1	Group 2	Group 3	Group 4
0.9% NaCl solution ($ml \cdot kg^{-1} \cdot h^{-1}$)	5.5	5	5	5
Glucose loading dose ($g \cdot kg^{-1} \cdot h^{-1}$)	0.0	0.1	0.2	0.3
n	10	10	10	10
Age (yr)	45.7 ± 16.6	40.8 ± 15.2	37.1 ± 16.5	41.0 ± 16.2
Sex (male/female)	3/7	3/7	3/7	5/5
Height (cm)	159.6 ± 9.8	157.2 ± 8.5	163.4 ± 9.8	160.4 ± 8.3
Weight (kg)	59.4 ± 8.0	52.9 ± 13.6	57.8 ± 10.7	56.7 ± 12.7
Body mass index ($kg \cdot m^{-2}$)	23.3 ± 2.4	21.2 ± 3.3	21.7 ± 4.2	22.0 ± 4.6
Surgical site (ear/surface)	8/2	8/2	3/7	10/0
Surgical duration (h)	2.2 ± 0.6	1.9 ± 0.4	2.2 ± 1.0	1.8 ± 0.6
Anaesthetic time (h)	3.2 ± 0.6	2.9 ± 0.3	3.2 ± 1.2	2.9 ± 0.6
Urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	1.6 ± 0.7	1.6 ± 1.4	1.2 ± 0.5	2.0 ± 1.7

Data are means ± SD. There were no significant differences among the groups

Table 2. Serial changes in parameters with the administration of glucose

Parameter	Group 1	Group 2	Group 3	Group 4
Plasma glucose ($mg \cdot dl^{-1}$)				
Preinduction	92.4 ± 11.4	91.2 ± 7.8	93.5 ± 9.5	94.5 ± 16.3
After induction of anesthesia	99.9 ± 9.7*	93.7 ± 13.6	97.1 ± 17.0	102.8 ± 24.0
1 h after additional infusion	108.5 ± 10.8**	122.2 ± 15.6**	143.0 ± 23.7**†	208.2 ± 49.3**†§¶
2 h after additional infusion	103.6 ± 12.1**	128.3 ± 22.8**	155.6 ± 28.5**†	261.3 ± 80.5**†§¶
Plasma insulin ($mU \cdot ml^{-1}$)				
Preinduction	4.15 ± 5.98	3.97 ± 4.98	3.06 ± 1.35	2.94 ± 2.04
1 h after additional infusion	3.28 ± 1.12	6.59 ± 6.06	11.12 ± 8.54*†	10.41 ± 7.59†
2 h after additional infusion	3.91 ± 2.67	9.58 ± 7.76	21.36 ± 14.88**†§	22.25 ± 12.40**†§
Serum free fatty acid ($mEq \cdot l^{-1}$)				
Preinduction	0.67 ± 0.23	0.73 ± 0.36	0.62 ± 0.19	0.81 ± 0.36
1 h after additional infusion	1.09 ± 0.35**	0.78 ± 0.23	0.82 ± 0.30*	0.74 ± 0.35
2 h after additional infusion	0.98 ± 0.27*	0.69 ± 0.32†	0.39 ± 0.21*†§	0.42 ± 0.28*†§
Serum β-Hydroxybutyric Acid ($mmol \cdot l^{-1}$)				
Preinduction	87.9 ± 17.3	80.3 ± 17.8	83.9 ± 14.7	86.0 ± 17.8
1 h after additional infusion	144.5 ± 45.9**	109.8 ± 36.7*†	85.3 ± 19.6†	89.6 ± 31.5†
2 h after additional infusion	142.5 ± 41.3**	91.3 ± 29.7†	55.9 ± 17.1**†§	52.2 ± 16.9**†§
Serum acetoacetic acid ($mmol \cdot l^{-1}$)				
Preinduction	69.8 ± 5.6	76.3 ± 14.6	72.2 ± 15.0	75.9 ± 12.6
1 h after additional infusion	79.9 ± 17.1	82.4 ± 14.0	67.5 ± 7.2†§	64.8 ± 5.3**†§
2 h after additional infusion	86.0 ± 19.0*	77.7 ± 13.8	61.9 ± 9.6*†§	61.1 ± 4.7**†§
AKBR				
Preinduction	0.82 ± 0.17	0.98 ± 0.21	0.87 ± 0.12	0.92 ± 0.24
1 h after additional infusion	0.59 ± 0.16**	0.82 ± 0.28	0.83 ± 0.22	0.83 ± 0.33
2 h after additional infusion	0.63 ± 0.16*	0.90 ± 0.20†	1.18 ± 0.32**†§	1.26 ± 0.34**†§
Urinary glucose excretion ($mg \cdot kg^{-1}$) during operation (2 h)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	3.0 ± 4.5†§¶

Data are means ± SD
* $P < 0.05$ vs. pre-induction value
** $P < 0.01$ vs. pre-induction value
† $P < 0.05$ vs. group 1 value
§ $P < 0.05$ vs. group 2 value
¶ $P < 0.05$ vs. group 3 value

infusion compared with the preanesthesia values. However, significant differences were observed between groups 1 and 3, groups 1 and 4, groups 2 and 3, groups 2 and 4, and groups 3 and 4 1 h after the start of the additional saline or glucose administration. The glucose load markedly increased the plasma levels of IRI in groups 3 and 4 at 2 h compared with the preanesthesia values. Significant differences were observed between

groups 1 and 3, groups 1 and 4, groups 2 and 3, and groups 2 and 4 2 h after the start of the additional saline or glucose administration.

Plasma concentrations of FFA were significantly elevated 1 and 2 h after the start of saline infusion in group 1. There was no significant change in FFA in group 2, whereas FFA levels declined significantly in groups 3 and 4. Significant differences were obtained between the values in groups 2, 3, and 4 versus group 1 2 h after the start of the additional infusion.

In β-HB, marked elevations were observed in group 1 1 and 2 h after the start of glucose infusion. Significant reductions in β-HB were observed in groups 3 and 4 2 h after the start of glucose infusion. AA were significantly increased 2 h after the start of saline infusion in group 1. On the other hand, AA were decreased significantly in groups 3 and 4. AKBR values fell markedly at 1 and 2 h in group 1, but increased significantly in groups 3 and 4.

There was no significant change in the plasma electrolyte concentration in any group.

The amounts of glucose excreted in the urine are shown in Table 2. No urinary glucose was detected in groups 1 and 2, and a slight amount was detected in a few subjects in group 3. The total amount of glucose lost was 3.0 g in group 4, calculated as 3% of the infused glucose.

Discussion

The major finding of the present study is that low doses of glucose (0.1–0.2 $g \cdot kg^{-1} \cdot h^{-1}$) prevented starvation without producing hyperglycemia during minor surgery under sevoflurane anesthesia. Our results showed that when glucose was not given, a catabolic state with lipolysis and ketosis developed even during minor surgery, which was associated with the consumption of energy substrates, leading to perioperative starvation. The results also revealed that 0.1–0.3 $g \cdot kg^{-1} \cdot h^{-1}$ of glucose, but not infusion of saline only, increased the excretion of insulin, indicating that insulin excretion is preserved under minor stress. However, a glucose dose of 0.3 $g \cdot kg^{-1} \cdot h^{-1}$, which does not usually provoke hyperglycemia or glucosuria under normal conditions, caused hyperglycemia even during minor surgery.

It is well known that during major surgery a high blood glucose level is precipitated by the activated sympathetic nervous system, reduced glucose tolerance, enhancing of glycogenolysis, and excretion of anti-insulin hormones. Kondo et al. have shown that glucose infusion at a rate of 0.184 $g \cdot kg^{-1} \cdot h^{-1}$ leads to hyperglycemia of 250 $mg \cdot dl^{-1}$ in patients undergoing gastrectomy under general anesthesia [8]. However, in the present study, a similar loading dose of glucose did not cause hyperglycemia. Therefore, the glucose tolerance of patients under general anesthesia is influenced by the severity of surgical stress. Hyperglycemia is thought to be a risk factor for the development of osmotic diuresis; exacerbation of brain, spinal cord [10], and renal damage due to ischemia [11]; delayed gastric emptying [11]; hypophosphatemia[11]; delayed wound healing [12,13]; and impaired white blood cell function [14]. During minor surgery, however, insulin secretion was induced by low doses of glucose without hyperglycemia.

The AKBR has been reported to decline in patients undergoing anesthesia and surgery after fasting [15]. AKBR values in the present study were depressed (0.63 in group 1 after 2 h of saline infusion) and recovered dose-dependently in groups 2, 3, and 4 up to 1.00. Ozawa et al. suggested that AKBR reflects the hepatic mitochondrial redox state and alterations of the rate of utilization of energy resources in surgical patients [9]. These findings suggest that glucose administration induces a high rate of utilization of glucose as an energy source in the hepatocyte.

Urinary excretion of glucose was observed only in group 4; the total amount was 3% of the glucose administered. Glycorrhea was due to an excess above the threshold for renal elimination. There were no significant differences between groups 3 and 4 in serum FFA and ketone bodies and AKBR after a 2-h administration of glucose. The rate of 0.3 $g \cdot kg^{-1} \cdot h^{-1}$ is in excess of the tolerance limit for glucose administration, even for patients under low surgical stress in this study.

Anesthetic agents would influence the metabolic degradation of energy resources. Nitrous oxide has been reported to change folic acid metabolism but not that of carbohydrates [16]. Saho et al. suggested that sevoflurane and nitrous oxide anesthesia do not alter carbohydrate metabolism in comparison with combinations of nitrous oxide and other fluorocarbon anesthetics [17]. However, sevoflurane has been reported to lower insulin excretion in patients under prolonged anesthesia [18]. It is possible that even 0.2 $g \cdot kg^{-1} \cdot h^{-1}$ of glucose would induce hyperglycemia during prolonged sevoflurane anesthesia. Further investigation is warranted.

In conclusion, a low dose of glucose at a rate of 0.1–0.2 $g \cdot kg^{-1} \cdot h^{-1}$ during minor surgery under sevoflurane anesthesia prevented hyperglycemia and the elevation of FFA and ketone bodies, and is considered to be optimal for minor surgery under sevoflurane anesthesia.

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