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ORIGINAL ARTICLE

Effects of intraoperative administration of carbohydrates during long-duration oral and maxillofacial surgery on the metabolism of carbohydrates, proteins, and lipids

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Abstract
Purpose Insulin resistance in patients undergoing invasive surgery impairs glucose and lipid metabolism and increases muscle protein catabolism, which may result in delayed recovery and prolonged hospital stay. We examined whether intraoperative administration of carbohydrates during long-duration oral and maxillofacial surgery under general anesthesia affects carbohydrate, proteins, and lipid metabolism and the length of hospital stay.
Methods We studied 16 patients with normal liver, kidney, and endocrine functions, and ASA physical status I or II, but without diabetes. Patients were randomly assigned to receive 0.1 g/kg/h of (n=8) or lactated Ringer's solution (n=8). Blood was collected before (T0) and 4 h after (T1) the start of surgery. We analyzed the plasma levels of glucose, ketone bodies, 3-methylhistidine (3-MH), and the length of hospital stay.
Results At T0, no statistically significant differences were observed in the levels of glucose, ketone bodies, and 3-MH between the groups. At T1, no statistically significant difference in glucose levels was found between the groups. However, ketone bodies were significantly lower, and the changes in 3-MH levels were significantly less pronounced in the glucose-treated group compared with controls. No significant differences were observed between the groups in terms of length of hospital stay.
Conclusions The administration of low doses of glucose during surgery was safe, did not cause hyperglycemia or hypoglycemia, and inhibited lipid metabolism and protein catabolism. Additional experiments with larger cohorts will be necessary to investigate whether intraoperative management with glucose facilitates postoperative recovery of patients with oral cancer.

Keywords Glucose · Intraoperative nutrition · Protein catabolism · General anesthesia · Oral and maxillofacial surgery

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Introduction

Patients with oral cancer who undergo oral and maxillofacial surgery sometimes have inadequate nutritional intake. In addition, patients who undergo invasive procedures, such as surgery, have facilitation of insulin resistance, which leads to a reduction of glucose utilization, enhancement of lipid metabolism, and protein loss due to catabolism (degradation) of proteins in the muscles. So far, intravenous extracellular fluid infusions without carbohydrates have conventionally been used during most surgical procedures [1]. However, the intraoperative loading of low doses of glucose has recently been reported to stimulate and promote insulin secretion, inhibit protein catabolism, and reduce the production of ketone bodies during surgery [2]. In addition, the emergence of ultrashort-acting narcotic analgesics, which provide a persistent and stable analgesic effect, has made it easier to achieve glycemic control and protect patients against stress caused by invasive surgery. Therefore, the issue of the perioperative anesthetic management of the patients should be readdressed, particularly in the context of nutritional management.

In this study, we examined the effects of the continuous intraoperative administration of low doses of carbohydrates for 4 h after the start of surgery on carbohydrate, protein, and lipid metabolism, protein loss, and the length of hospital stay in patients with oral cancer.

Materials and methods

The study consisted of 16 patients, mainly with oral cancer, who underwent long-duration surgery (4 h or longer) at the Department of Surgery of the Kyushu Dental University Hospital in Kitakyushu, Japan. We included patients without diabetes, with normal liver, kidney, and endocrine functions, and with physical status I or II according to the American Society of Anesthesiologists' classification system. All patients provided written informed consent to participate in the study, and the study was approved by the Research Ethics Committee at the Kyushu Dental University under code number 23-27. Written informed consent was obtained from all the patients.

Patients were randomly assigned to two groups using the envelope method. One group received glucose during surgery (glucose group, $n=8$) and the other did not (control group, $n=8$) (Table 1). The type of surgery the patients underwent is shown in Table 1.

In both groups, Lactated Ringer's solution containing no carbohydrates was used for intravenous infusions (Lactec® injectable solution, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). In the glucose group, injectable glucose solution (50 % solution, Otsuka Pharmaceutical Co., Ltd.) was diluted to 5 % concentration and administered from the side tube of the infusion line at an infusion rate of 0.1 g glucose/kg/h using a syringe pump (Terufusion syringe pump, ®TE-332S, Terumo, Tokyo, Japan).

On the day before surgery, patients were instructed to refrain from eating and drinking for 12 h. On the day of surgery, after induction of general anesthesia, indwelling catheter was placed in the radial artery of the arm or the dorsal artery of the foot. Arterial pressure was measured and blood samples were obtained by inserting a catheter in the artery. Blood was collected before surgery (T0) and 4 h after the start of surgery (T1). In the glucose group, blood collection at T0 was followed by administration of glucose (0.1 g/kg/h). The blood collected from the arterial catheter was used to measure the plasma levels of glucose (normal range, 80–180 mg/dL), ketone bodies (indicators of lipid metabolism, normal range, 28~120 μmol/l), and 3-methylhistidine (3-MH; an indicator of muscle protein catabolism, normal range unknown). In this study, we investigated whether the administration of low doses of carbohydrates causes hypoglycemia or hyperglycemia, suppresses the production of ketone bodies and 3-MH is suppressed, and shortens the length of hospital stay.

For general anesthesia, the same method was used in both groups. Induction was performed using an intravenous anesthetic (propofol, 1~1.5 mg/kg) and a muscle relaxant (rocuronium bromide, 0.6 mg/kg), followed by O_2 (40 %) and an inhalational anesthetic (sevoflurane, 1~1.5 %). Anesthesia was maintained using an ultrashort-acting narcotic analgesic (remifentanil, 0.2~0.3 μg/kg/min). The patient's condition was managed so that the bispectral index (Aspect Medical Systems Inc, Newton, MA) ranged between 40 and 60 during surgery. In addition, when plasma glucose levels reached 200 mg/dL or higher during surgery, glycemic control using insulin was initiated.

Statistical analyses were conducted using the IBM SPSS Statistics software. Among the background factors used in the

Table 1 Characteristics of the study groups

	Control group (mean±SD)	Glucose group (mean±SD)	*P* value
Age (years)	63±13	66±16	0.73
Sex (male/ female)	6/2	6/2	1.00
Height (cm)	163.1±11.1	163.0±8.2	0.73
Weight (kg)	74.0±31.2	53.3±4.7	0.12
Body mass index (kg/m^2)	26.4±7.8	20.3±1.4	0.08
Amount of adrenaline used (μg)	120.6±65.3	90.8±33.5	0.32
Amount of ephedrine used (mg)	14.8±8.6	16.5±9.2	0.81
Volume of infusion (mL/kg/h)	4.3±1.2	5.7±1.4	0.10
Urine output (mL/kg/h)	1.1±0.8	1.2±0.4	0.84
Catheter placed artery (radial/dorsal)	5/3	6/2	0.50
Type of surgery	Neck dissection: 1	Open reduction and internal fixation: 1	
	Tumor resection: 7	Tumor resection: 7	

No significant differences were observed between the groups for any of the parameters comparisons between the groups, sex was tested using the Fisher exact test, while the other parameters including the plasma levels of glucose, ketone bodies, 3-MH, and the length of hospital stay were tested using the unpaired *t* test. The 3-MH results are shown as the change in level from T0 and T1. A *P* value of less than 0.05 was considered statistically significant.

Results

No significant differences were observed between the groups in terms of age, body weight, and sex. Moreover, the amounts of adrenaline added to the local anesthetics and of sympathomimetic drug, alpha-agonist vasopressors (ephedrine), used during surgery were similar in both groups (P=0.32 and P=0.81, respectively) (Table 1).

No significant differences were observed between the groups in any of the parameters, hemodynamic status (heart rate, mean body pressure) and bispectral index values at baseline (T0) and 4 h after the start of surgery (T1) (Table 2).

At T0, there were no significant differences between the groups in terms of the plasma levels of glucose, ketone bodies, and 3-MH. At T1, there were no significant differences between the groups only in plasma glucose levels (P=0.065) (Fig. 1). In the control group, the concentrations of ketone bodies at T1 were significantly higher compared with those at T0 (P=0.022). In addition, at T1, the plasma concentrations of ketone bodies were significantly lower in the glucose group than in the control group (P=0.021) (Fig. 2). The changes in plasma 3-MH levels were significantly lower in the glucose group than in the control group (P=0.047) (Fig. 3). No significant differences were observed between the groups in terms of the length of hospital stay (P=0.198; Fig. 4).

Table 2 Hemodynamic status and bispectral index values at baseline (T0) and 4 h after the start of surgery (T1)

	T0	T1	*P* value
Heart rate (bpm)			
Control group	67±6	65±6	0.39
Glucose group	57±7	57±4	0.92
MBP (mmHg)			
Control group	98±6	101±4	0.15
Glucose group	96±14	98±8	0.42
BIS values			
Control group	46±6	47±4	0.60
Glucose group	45±3	46±1	0.70

No significant differences between two groups were detected for any of the parameters

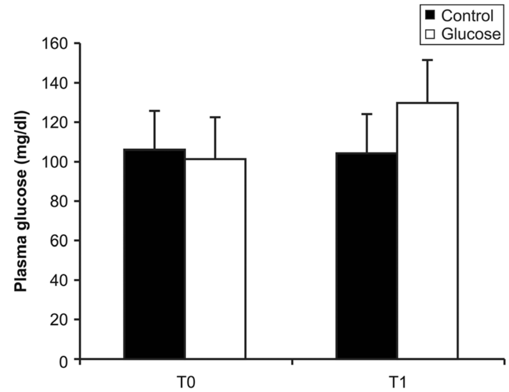

Fig. 1 Plasma glucose level for glucose group and control group patients at anesthetic induction (T0) and 4 h after the start of surgery (T1). Differences between groups and within groups were not significant (NS) for plasma glucose levels. Results are expressed as mean±standard deviation (SD)

Discussion

Our findings showed that in oral and maxillofacial surgery, the perioperative administration of low doses of glucose allowed inhibition of lipid metabolism and protein catabolism, without causing excessive hyperglycemia or hypoglycemia.

The intravenous infusion rate of the injected glucose depends on the intravenous infusion load and is thus subject to changes owing to hypotension after anesthetic induction or owing to sudden bleeding. Thus, we expected that the administration of glucose at a constant rate would not be possible. Therefore, we used a syringe pump to administer glucose accurately at a determined infusion rate. In addition, a previous study on rats [3] showed no differences in terms of the inhibitory effect on protein catabolism between glucose administration rates of 0.1 and 0.5 g/kg/h. Therefore, we chose the administration rate of 0.1 g/kg/h. We also chose this rate because intravenous administration of high-concentration glucose solution (10 % or more) is likely to trigger thrombophlebitis owing to high osmolarity. In this study, no patient

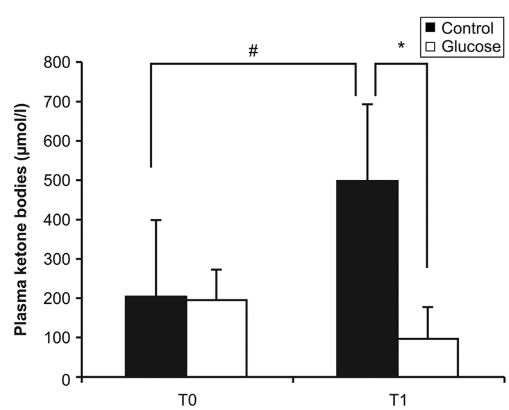

Fig. 2 Differences in the plasma levels of ketone bodies between the groups. #P<0.05 within the groups and *P<0.05 between the groups (unpaired *t* test). Results are expressed as mean±standard deviation (SD)

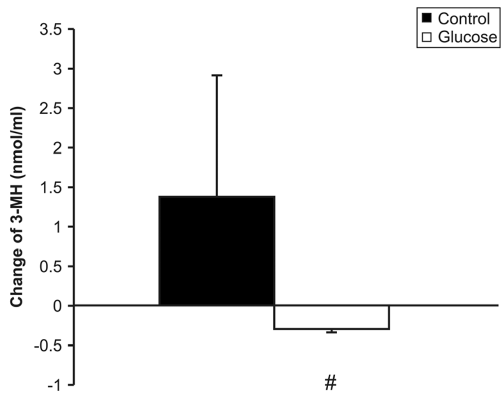

Fig. 3 Change in plasma 3-methylhistidine (3-MH) levels from T0 to T1. #$P<0.05$ between the groups (unpaired t test). Results are expressed as mean±standard deviation (SD)

experienced thrombophlebitis. The diluted glucose concentration was 5 %, and the administration rate was 0.1 g/kg/h, which was thought to reduce the risk of patients developing postoperative thrombophlebitis.

The administration of adrenaline causes an increase in plasma glucose levels; however, in this study, no significant differences were observed between the groups in terms of the amount of adrenaline added to the local anesthetic and the doses of sympathomimetic drug, alpha-agonist vasopressors (ephedrine). Corticosteroids were not used in any of the groups during the study period. In this study, plasma glucose levels did not reach ≥200 mg/dL during surgery; therefore, it was not necessary to administer insulin.

Previous reports have shown that it is best to assess variations in 3-MH levels by measuring its plasma levels than urinary levels because plasma levels reflect short-term changes [4]; therefore, in our study, we measured the plasma levels of 3-MH along with those of glucose and ketone bodies.

Excessive hyperglycemia causes damage to the cellular functions of vascular endothelial cells and the phagocytic function of monocytes, which leads to a delay in wound healing and increases the postoperative risk of infection. The incidence of surgical wound infection has been reported to be high in patients with intraoperative plasma glucose levels of 150 mg/dL or higher [5]. Fifty percent of patients with

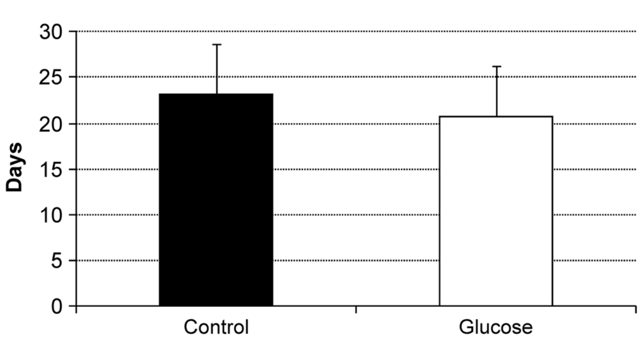

Fig. 4 Length of hospital stay. Results are expressed as mean±standard deviation (SD). Difference between the groups were not significant (NS)

diabetes have been reported to experience deterioration in glycemic control after oral surgery under general anesthesia. In 30 % of the cases, the deterioration persisted for 3 days or longer after the surgery [6]. This confirms the importance of glycemic control in the perioperative period [7–9].

However, previous reports have shown that 60 % of glucose is produced through gluconeogenesis as a result of 22-h fasting, which starts on the day before surgery [10]. This suggests that, preoperatively, patients with oral cancer are in a state of biological starvation. Intraoperative administration of glucose not only causes an increase in plasma glucose levels but also inhibits protein catabolism [11]. In our study, we also observed an inhibitory effect of glucose on protein catabolism. Previous studies have shown that when surgery lasts longer than 3 h, the production of ketone bodies is enhanced; therefore, to inhibit the disintegration of muscle proteins, a minimum amount of carbohydrates needs to be administered even if the surgery is conducted under general anesthesia [12]. The use of oral carbohydrates has been reported to be safe and well tolerated and was not found to cause any perioperative adverse events. Moreover, they were found to improve postoperative metabolism by decreasing insulin resistance [13]. Thus, screening for various perioperative management techniques such as administration of lose doses of carbohydrates could improve the quality of life of oral cancer patients.

In conclusion, during the perioperative period, the patient is in a state of biological starvation and develops a stress response to invasive surgery, resulting in enhanced gluconeogenesis and insulin resistance by inflammatory cytokines, which leads to stress-induced hyperglycemia. However, reducing stress by providing sufficient analgesia, preventing hyperglycemia, and providing an adequate amount of glucose and appropriate glycemic control, may facilitate quick recovery in postoperative patients. Our study suggests that the administration of low doses of glucose during oral and maxillofacial surgery is safe, does not cause excessive hyperglycemia or hypoglycemia, and inhibits lipid metabolism and protein catabolism. In this study, we could not determine whether these surrogate measures could predict patient outcomes and directly facilitate clinical healing in terms of the length of hospital stay. The main limitation of our study was the small sample size in both groups. Additional studies with a larger cohort will be necessary to validate the finding that intraoperative management with glucose facilitates postoperative recovery of patients with oral cancer.

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Conflict of interest The authors have no conflict of interest to declare.

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References

1. Kadoi Y (2010) Anesthetic consideration in diabetic patients Part II: intraoperative and postoperative management of patients with diabetes mellitus. J Anesth 24:748–756
2. Yamasaki K, Inagaki Y, Mochida S, Funaki K, Takahashi S, Sakamoto S (2010) Effect of intraoperative acetated Ringer's solution with 1% glucose on glucose and protein metabolism. J Anesth 24:426–431
3. Mikura M, Yamaoka I, Doi M, Kawano Y, Nakayama M, Nakao R, Hirasaka K, Okumura Y, Nikawa T (2009) Glucose infusion suppresses surgery-induced muscle protein breakdown by inhibiting ubiquitin-proteasome pathway in rats. Anesthesiology 110:81–88
4. Yamashita S (2007) Plasma 3-methyl histidine as a standard for muscular proteolysis: normal range of plasma 3-methyl histidine in healthy adults and comparison to that of critically ill patients. Yamaguchi Med J 56:193–200 **[Article in Japanese]**
5. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A (2003) Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 125:1007–1021
6. Fujikawa M, Takada Y, Tateishi A et al (1998) Effects of an oral and maxillofacial surgery under a general anesthesia on diabetic control. J Kyushu Dent Soc 52:245–250 **[Article in Japanese]**
7. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR (2008) Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 359:1565–1576
8. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N (2009) Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 373:1765–1772
9. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 359:1577–1589
10. Rothman DL, Magnusson I, Katz LD, Shulman RG, Shulman GI (1991) Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13c NMR. Science 254:573–576
11. Lattermann R, Carli F, Wykes L, Schricker T (2003) Perioperative glucose infusion and the catabolic response to surgery: the effect of epidural block. Anesth Analg 96:555–562
12. Yokoyama T, Suwa K, Yamasaki F, Yokoyama R, Yamashita K, Sellden E (2008) Intraoperative infusion of acetated Ringer solution containing glucose and ionized magnesium reduces ketogenesis and maintains serum magnesium. Asia Pac J Clin Nutr 17:525–529
13. Gawecka A, Mierzewska-Schmidt M (2014) Tolerance of, and metabolic effects of, preoperative oral carbohydrate administration in children - a preliminary report. Anaesthesiol Intens Ther 46:61–64