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ORIGINAL ARTICLE

Effect of intraoperative acetated Ringer's solution with 1% glucose on glucose and protein metabolism

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Abstract
Purpose To investigate the effects of the intraoperative administration of Ringer's solution with 1% glucose on the metabolism of glucose, lipid and muscle protein during surgery.
Methods Thirty-one adult patients, American Society of Anesthesiologists physical status I or II, undergoing elective otorhinolaryngeal, head and neck surgeries were randomly assigned to one of two patient groups: those receiving acetated Ringer's solution with 1% glucose (Group G) or those receiving acetated Ringer's solution without glucose (Group R) throughout the surgical procedure. Plasma glucose was measured at anesthetic induction (T0), artery 1 h (T1), 2 h (T2), 3 h after anesthetic induction (T3) and at the end of surgery (T4). Plasma ketone bodies, insulin and 3-methylhistidine were measured at T0 and T4.
Results The intravenous infusion for patients in Group G and R was 6.1 ± 0.8 and 6.3 ± 1.7 ml/kg/h, respectively, with Group G patients receiving a dose of 4.1 g/h glucose. Plasma glucose levels were significantly higher in Group G than in Group R patients at T1, T2, T3 and T4; however, plasma glucose remained <150 mg/dl in both groups. The plasma concentration of ketone bodies was significantly higher ($P < 0.05$) in Group R than in Group G patients at T4. Changes in plasma 3-methylhistidine concentration was significantly lower in Group G than in Group R patients. These results indicate that acetated Ringer's solution with 1% glucose decreased protein catabolism without hyperglycemia among the Group G patients.
Conclusion The infusion of a small dose of glucose (1%) during minor otorhinolaryngeal, head and neck surgeries may suppress protein catabolism without hyperglycemia and hypoglycemia.

Keywords Glucose · Intraoperative nutrition · 3-Methylhistidine · Protein metabolism

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Introduction

The results of a number of studies have led to the proposal that the administration of glucose may not always be necessary during surgical procedures because of glucose intolerance caused by the surgical stress response [1–4]. Hyperglycemia often occurs during the administration of conventional fluid with 2.5, 5 or 10% glucose during surgery [3–7]. However, hypoglycemia during the surgical procedure activates the sympathetic nervous system and pituitary–adrenal response, thereby accelerating the catabolism of protein and fat due to the production of glucose. In addition, preoperative fasting contributes to the increase of protein breakdown that is usually observed in surgical patients and to the cumulative decrease of glycogen in the liver [2, 8]. Although glucose administration is known to suppress the production of glycogen in the liver and protein, the addition of glucose to the infusion for preserving the protein level during surgical procedures has been controversial [3, 5, 9, 10], with the results of several studies suggesting that hyperglycemia in this perioperative period could be harmful [11–13]. Moreover, a recent concept in

the management of critically ill patients is to maintain the plasma glucose concentration at 110–180 mg/dl [14–16].

We hypothesized that the administration of a small dose (1%) of glucose—not 5% glucose—may preserve the protein level during surgery without an increase in the plasma glucose concentration. We therefore conducted a prospective randomized control study to test our hypothesis and clarify the significance of glucose administration under the conditions of surgical stress.

Materials and methods

After obtaining approval from the Ethics Committee of Tottori University Faculty of Medicine, we obtained written informed consent from all 31 patients, American Society of Anesthesiologists physical status I or II, who underwent elective otorhinolaryngeal, head and neck surgery. Patients with diabetes and/or obesity [body mass index (BMI) >25 kg/m] were excluded from the study. Patients were allocated into one of two groups by computer-generated random code: Group G, consisting of 16 patients who were infused with acetated Ringer's solution with 1% glucose; Group R, consisting of 15 patients who were infused with the same solution but without glucose. After fasting overnight with no intravenous (IV) fluid administration—no patients were premedicated—general anesthesia was induced by 2 mg/kg propofol, 0.02 mg/kg fentanyl and 0.1 mg/kg of vecuronium bromide and maintained with sevoflurane, 40% oxygen and intermittent doses of fentanyl to maintain bispectral index (BIS) levels <60.

Group G patients were infused with acetated Ringer's solution with 1% glucose during anesthesia while Group R patients were infused with acetated Ringer's solution without glucose during the same period. The infusion rate was freely adjusted by the anesthesiologist in charge according to the situation of surgery until the end of surgery. Insulin therapy was permitted intraoperatively at a plasma glucose level >180 mg/dl. Other fluids, such as plasma or colloids, were not permitted with the exception of 100 ml of saline to dilute antibiotics.

Measurements

Blood samples were collected from the vein on the opposite side of infusion at anesthetic induction (T0) and from the radial artery 1 h (T1), 2 h (T2), 3 h after anesthetic induction (T3) and at the end of surgery (T4) to determine plasma glucose. Ketone bodies (acetoacetate and betahydroxybutyrate), insulin and 3-methylhistidine (3-MH) were measured at T0 and T4. The blood samples were centrifuged at 3,000 rpm for 10 min and the serum and plasma obtained were frozen (−20°C) until analysis. Plasma glucose (ABL System 625; Radiometer, Copenhagen, Denmark) were measured at the same time. Ketone bodies were measured by enzymatic techniques. The plasma insulin (normal range: 3.06–16.9 μU/ml) level was determined by radioimmunoassay, and the plasma 3-MH level was measured by high-performance liquid chromatography.

Statistics

Data values are expressed as mean ± standard deviation (SD). Nonparametric variables were compared between the groups using χ^2 test. Parametric data were compared between the groups using unpaired t test. Plasma glucose, hemodynamic data and BIS values were analyzed using two-way analysis of variance with repeated measures. When a significant difference was noted, the Bonferroni–Dunn test was performed for multiple comparisons. $P < 0.05$ was considered to be statistically significant.

Results

No patients were administered insulin, and no other fluids, such as blood or colloids, were administered, with the exception of 100 ml of saline for diluting the antibiotics. There were no significant differences between the two patient groups in terms of demographic data (Table 1) and types of surgeries (Table 2). There were also no significant differences between the groups in hemodynamic status and BIS values (Table 3).

Group G patients received acetated Ringer's solution with 1% glucose at a rate of 6.1 ± 0.8 ml/kg/h; those in

Table 1 Characteristics of the study population

Demographic characteristics	Group G ($n = 16$)	Group R ($n = 15$)
Male/female	7/9	9/6
Age (year)	55 ± 16	54 ± 17
Height (cm)	161 ± 11	161 ± 11
Weight (kg)	59 ± 10	63 ± 8
BMI (kg/m^2)	22.8 ± 2.6	23.5 ± 3.3
Fasting time (min)	843 ± 115	784 ± 132
Anesthesia time (min)	227 ± 75	240 ± 93
Fentanyl (μg/kg)	5.1 ± 1.0	5.8 ± 0.9
Infusion (ml/kg/h)	6.1 ± 0.8	6.3 ± 1.7
Urine output (ml/kg/h)	1.9 ± 0.9	1.8 ± 1.1

Values are given as the mean ± standard deviation (SD). Nonparametric variables were compared between groups using χ^2 test. Parametric data were compared between groups using an unpaired t test. There were no significant differences between groups

BMI Body mass index

Table 2 Types of surgery

Group G (acetated Ringer's solution with 1% glucose)	$n = 16$	Group R (acetated Ringer's solution without glucose)	$n = 15$
Submandibular gland extirpation	3	Submandibular gland extirpation	3
Tympanoplasty	2	Tympanoplasty	3
Endoscopic sinus surgery	2	Endoscopic sinus surgery	2
Partial glossectomy	2	Tonsillectomy	2
Tonsillectomy	1	Total thyroidectomy	1
Neck dissection	1	Retinal reattachment surgery	1
Cleft lip repair	1	Otoplasty	1
Lipoma extirpation	1	Maxillectomy	1
Other tumor extirpation of oral cavity	3	Other tumor extirpation of oral cavity	1

Table 3 Hemodynamic status and BIS values of patients

Hemodynamic status and BIS values	T0 (16/15)[a]	T1 (16/15)	T2 (16/15)	T3 (11/11)	T4 (16/15)
HR (bpm)					
Group G	70 ± 11	64 ± 8	63 ± 6	61 ± 6	75 ± 9
Group R	68 ± 9	64 ± 12	67 ± 9	66 ± 9	77 ± 19
MAP (mmHg)					
Group G	97 ± 15	68 ± 10	74 ± 12	73 ± 11	91 ± 12
Group R	96 ± 14	70 ± 12	81 ± 10	79 ± 8	90 ± 18
BIS values					
Group G		46 ± 9	44 ± 10	49 ± 10	
Group R		45 ± 8	46 ± 6	45 ± 5	

Values are given as the mean ± SD. There were no significant differences between groups two-way analysis of variance with repeated measures

T0 Anesthetic induction, *T1* 1 h, *T2* 2 h, *T3* 3 h after anesthetic induction, *T4* at the end of surgery, *HR* heart rate, *MAP* mean arterial pressure, *BIS* bispectral index

[a] Numbers in parenthesis are the number of Group G patients/number of Group R patients

Group R received acetated Ringer's solution at a rate of 6.3 ± 1.7 ml/kg/h. Group G patients received a dose of 4.1 g/h glucose.

Figure 1 shows that plasma glucose levels were significantly higher in Group G than in Group R patients at T1, T2, T3 and T4. In Group G patients, the glucose levels were significantly higher at T1, T2, T3 and T4 than at T0. Mean plasma glucose levels ranged from 93.8 ± 6.4 mg/dl at T0 to 114 ± 11.6 mg/dl at T4 in Group G patients and from 94.3 ± 7.9 mg/dl at T0 to 101.2 ± 11.6 mg/dl at T4 in Group R patients. The minimum glucose value was 88 and 83 mg/dl in Group G and R patients, respectively; the maximum glucose value was 145 and 126 mg/dl, respectively (Fig. 1).

The plasma concentration of ketone bodies was significantly higher ($P < 0.05$) in Group R than in Group G patients at T4. In Group R, the plasma concentration of ketone bodies was significantly higher at T4 than at T0. There were no significant differences between the groups in terms of plasma insulin concentration throughout the study period (Fig. 2).

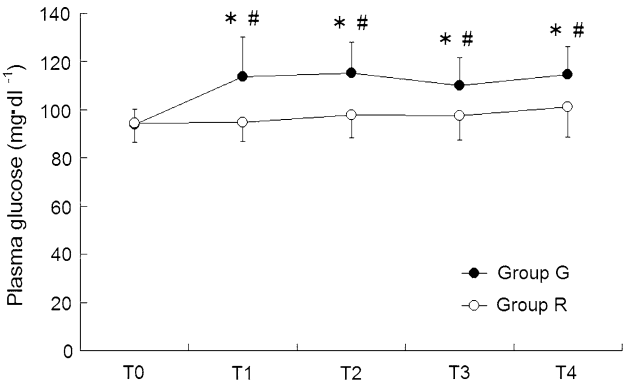

Fig. 1 Plasma glucose concentrations for Group R and Group G patients at anesthetic induction (*T0*), 1 h (*T1*), 2 h (*T2*) and 3 h after anesthetic induction (*T3*) and at the end of surgery (*T4*). Differences between groups were significant for plasma glucose concentration at $P < 0.05$ by two-way analysis of variance (ANOVA) with repeated measures between groups. $^{*}P < 0.005$ versus T0 by Bonferroni–Dunn test; $^{\#}P < 0.05$ between groups by unpaired *t* test

Changes in plasma 3-MH concentrations during surgery in Group G patients were significantly lower than those in Group R patients by the unpaired *t* test (Fig. 3).

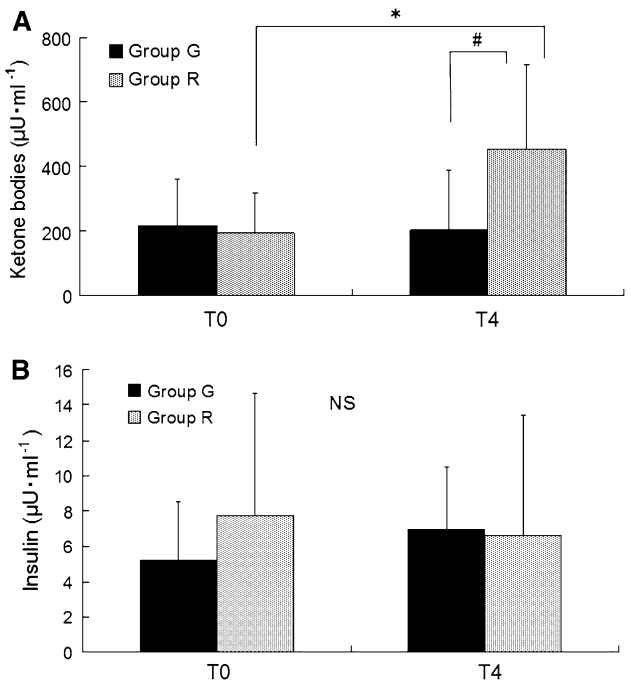

Fig. 2 Plasma ketone body (**a**) and plasma insulin concentrations (**b**) for Group R and Group G patients at anesthetic induction (*T0*) and the end of surgery (*T4*). $^{\#}P < 0.05$ between groups and $^{*}P < 0.05$ within groups by the unpaired *t* test for plasma ketone body concentration. Differences between groups and within groups were not significant (*NS*) for plasma insulin concentration. Results are expressed as the mean ± standard deviation (SD)

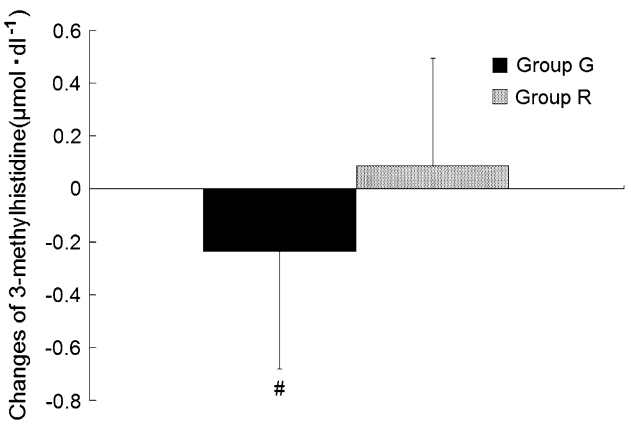

Fig. 3 Changes in plasma 3-methylhistidine concentrations. $^{\#}P < 0.05$ between groups by unpaired *t* test. Results are expressed as mean ± SD

Discussion

The results of this study demonstrate that the administration of acetated Ringer's solution with 1% glucose attenuated protein catabolism without hyperglycemia of more than 150 mg/dl and proved our hypothesis on protein metabolism during surgery. Solutions containing 2.5, 5 or 10 glucose were often used in previously reported studies, and these were found to cause hyperglycemia of >180 mg/dl during their infusions [3–7]. The acetated Ringer's solution with 1% glucose infused in our study did not increase plasma glucose concentrations >150 mg/dl, suggesting that a small infusion of glucose may attenuate protein catabolism within the safe range of plasma glucose. All endocrine and metabolic changes due to surgical stress contribute to high plasma glucose concentrations in the presence of glucose infusion [2, 6, 17–19]. In this study, the surgical stress that the patients experienced was considered to be similar between the two study groups because the dosage of fentanyl used was similar; the infusion rate was also similar. These findings indicate that both an infusion of acetated Ringer's solution with 1% glucose, which provided enough fluid to patients undergoing otorhinolaryngeal, head and neck surgeries, as well as an infusion of acetated Ringer's solution without glucose were useful in terms of attenuating the increase in plasma glucose concentration during surgery. We did not measure the levels of catecholamines as an indication of the degree of stress of our surgical patients. Stress hormones are released in a large part by the activation of the sympathetic nervous system due to strong nociceptive stimuli. The similar hemodynamic status and BIS values provided by a similar dosage of fentanyl between the two groups suggest that plasma levels of stress hormones or catecholamines in the patients were most likely the same.

Patients in Group R, who received the non-glucose solution, had high levels of ketones during anesthesia, but none of these patients showed hypoglycemia during surgery. These findings indicate that fat was resolved during surgery to produce energy in the cell. In comparison, the lack of significant alterations in the ketone bodies of Group G patients was likely due to exogenous glucose suppressing the resolution of fat. Our results demonstrate that even minor surgeries can disturb physiological metabolism. Therefore, the correction of metabolism during anesthesia may be important to provide better postoperative results.

An increase in protein catabolism can be suspected in the glucose-free group (Group R) due to a lack of the nitrogen-sparing effect of glucose after surgery [20–22]. The administration of exogenous glucose is thought to suppress protein catabolism during surgery and preserve muscle protein. However, the use of glucose during the acute phase of surgical tissue trauma has produced conflicting results [3, 9, 10]. In one study, intravenous glucose did not improve the nitrogen balance in patients undergoing craniotomy [3], and in another study, glucose infused at a rate of about 10 g/h during cholecystectomy did not affect the plasma concentration of branched-chain amino acids (BCAA), indicating inhibition of whole-body protein breakdown [9]. On the other hand, the IV administration of glucose at a rate of 10 g/h during gastrectomy was found to

decrease the plasma concentration of BCAA [10] and amino acid oxidation, indicating a protein-sparing effect [5]. 3-MH is an amino acid derived from the resolution of muscle and a marker for muscle catabolism. Although other amino acids are reused for synthesizing a new protein, 3-MH is not reused at all and is extracted from the kidneys. In our study, there was no significant difference in the plasma concentration of 3-MH between the two study groups. However, the plasma concentration of 3-MH was significantly reduced in Group G patients. The observed alterations in the 3-MH level from anesthetic induction to the end of anesthesia in Group G patients, namely, a significant decrease, indicate a suppression of muscle resolution, which is a protein-sparing effect. 3-MH is usually measured in the urine. Renal function could affect the value of 3-MH. Nagasawa et al. [23] also suggest that plasma 3-MH is a sensitive index of myofibrillar protein degradation. Consequently, it was measured using blood samples in this study.

Skeletal muscle is the main source of degraded protein after surgery, and the 3-MH level is considered to be a reliable indicator of the skeletal muscle protein breakdown rate [24, 25]. However, according to recent reports, muscle protein breakdown begins after the first 24 h post-surgery, and the protein donor during the early response to surgery should mainly be of intestinal origin (smooth muscle) rather than skeletal muscle [26–28]. The results of our study confirm that surgical stress and fasting in Group R patients increased the concentration of 3-MH. Many investigators have suggested that muscle breakdown actually increases after major surgery, based on their interpretation of increases in urinary 3-MH excretion [29–31]. However, López-Hellín et al. [26] reported that 3-MH excretion did not increase after surgery.

There are some limitations to our study. Propofol was used to induce general anesthesia. While the lipid components of propofol may have had an effect on some of the metabolic parameters measured, we do not believe that it had an effect on the difference between groups because the dosage of propofol was similar for the two groups. Second, although the hemodynamic status and BIS values were similar between the two groups, we cannot ignore that fact that there may have been a bias between groups in terms of the wide variation in surgical procedures and level of stimulation. Third, the number of patients included in our study is relatively small, so larger studies are necessary to clarify whether muscle breakdown is inhibited by the infusion of acetated Ringer's solution with 1% glucose.

In terms of glucose metabolism, the most important factor is the dose of glucose administered. In this study, the infusion rate was not constant, which may have influenced the glucose concentration. However the average amount of glucose was about 4.1 g/h, which is not so small when compared to the commonly used dose of 5 g/h but considerably less than the dosage reported in previous studies (10 g/h). Moreover, a constant glucose infusion has seldom been used in the clinical anesthesia setting except for patients with diabetes mellitus. Therefore, we administered the 1% glucose solution under conditions standard to the clinical anesthesia setting.

Our aim was to investigate the metabolism of glucose, fat and protein during minor surgery using Ringer's solution with 1% glucose. Based on our results, we conclude that the infusion of a small dose of glucose (1%) during surgery is likely to suppress protein catabolism in minor surgery. This conclusion has meaningful consequences for perioperative infusion therapy. However, it is glucose metabolism in major surgery that is considered to be the most serious problem and, consequently, further study is required with high-dose glucose solutions in this setting. The benefits of the 1% glucose-containing solution can then be determined by comparing these with data obtained using higher dose glucose solutions. In this context, Mikura et al. [32] reported that the IV infusion of 1 or 5% glucose significantly suppressed the increase in excretion of urinary nitrogen and 3-MH in rats, with no difference in the inhibitory effects between the two glucose groups.

In conclusion, an infusion of acetated Ringer's solution with 1% glucose during minor otorhinolaryngeal, head and neck surgeries did not result in either hyperglycemia or hypoglycemia and suppressed the resolution of both fat and protein. We conclude that the infusion of a small dose of glucose (1%) during surgery may suppress protein catabolism.

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