Original Article

Intraoperative infusion of acetated Ringer solution containing glucose and ionized magnesium reduces ketogenesis and maintains serum magnesium

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The effect of glucose infusion during surgery on glucose metabolism has not been investigated sufficiently. We, therefore, examined the effect after the infusion of 1% glucose acetated Ringer solution containing Mg^{2+} during surgery on ketogenesis and serum Mg^{2+} concentrations. Patients, classified as ASA I-II, age 51-80 years, were randomly assigned to receive infusion of acetated Ringer solution. The G/Mg group received infusion with 1% glucose, Na^{+} 140mEq/L, Mg^{2+} 2 mEq/L, and the C group received infusion with glucose free solution containing Na^{+} 130 mEq/L without Mg^{2+}. Both solutions were infused at a rate of 25 mL/kg for the first hour, and maintained at 4 mL/kg/hr thereafter. Blood samples were collected three times: before infusion and at 1 hour and 4 hours after the start of infusion. Electrolytes and glucose metabolism were evaluated at each sampling. After rapid infusion, blood glucose level significantly increased to 170±19mg/dL in the G/Mg group, but it returned to close to baseline after 4 hours and serum ketone bodies did not increase during infusion. In the C group, however, blood glucose never increased beyond 110 mg/dL, but both acetoacetic and hydroxybutyric acids increased significantly at the third measurement.

Key Words: perioperative infusion, glucose metabolism, ketogenesis, insulin, magnesium

INTRODUCTION

Insulin resistance is one of major problems for patients undergoing elective surgery since hyperglycemia increases morbidity and mortality (1). It has been reported that the development of insulin resistance is associated with the magnitude of surgery (2,3) and that preoperative administration of carbohydrates attenuates postoperative insulin resistance (4-6). In addition, perioperative insulin and glucose infusion also maintains insulin sensitivity after surgery (7). Intraoperative hyperglycemia caused by glucose infusion augments reperfusion tissue damage (8,9). The effect of perioperative glucose infusion without exogenous insulin on glucose metabolism, however, has not been investigated sufficiently. Elective surgery is usually performed after overnight fasting for more than 12 hours. Even in young subjects, more than one-third of glucose production depends on gluconeogenesis after 22 hours of fasting (10). Therefore, preoperative fasting may be long enough to change the metabolic situation and increase ketogenesis.

Ionized magnesium (Mg^{2+}) is a cofactor required for the energy-dependent membrane pumps controlling electrolyte gradients (11,12). The fluid given intravenously reduces the activity of the cations as it does the concentration of protein and red blood cell count. In anesthetized patients, hypomagnesemia may exacerbate pre-existing cardiovascular disease (13).

We hypothesized that acetated Ringer solutions containing low concentrations of glucose and Mg^{2+} may prevent the development of ketogenesis and maintain serum magnesium concentration. We examined, therefore, the alteration of serum Mg^{2+} concentration and serum ketone bodies during surgery in the patients infused with 1% glucose acetated Ringer solution containing 2mEq/L of Mg^{2+} and those infused with acetated Ringer solution not containing glucose or magnesium.

MATERIALS AND METHODS

After approval by the institutional Review Board of Kochi Medical School Hospital, written informed consent was obtained from a total of 26 patients (ASA class I-II, aged

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51-80 yr) who were undergoing orthopedic surgery for more than 4 hours. Exclusion criteria included diabetes mellitus, abnormality in serum electrolytes and body weight of less than 40 kg or more than 80 kg. All patients were randomly assigned to receive infusion of acetated Ringer solutions of one of the following two types; the G/Mg group received the solution with 1% glucose, Na^+ 140 mEq/L and Mg^{2+} 2mEq/L, (Physio140^{TM}, Otsuka, Japan) (G/Mg solution) and the C group received the solution without glucose and Mg^{2+} but with Na^+ 130 mEq/L (Veen F^{TM}, Nikkenkagaku, Japan) (C solution). Fifteen mL of blood were collected from the antebrachium vein at three time intervals: before infusion, at 1 hour- and 4 hours after the start of infusion.

Nothing was given per os for 12 hours before anesthesia. No patients received premedication. After taking the blood sample for the first measurement (baseline), anesthesia was induced by intravenous midazolam 0.1 mg/kg and inhalation of 5% sevoflurane in 6 L/min of 100% oxygen. Four % lidocaine was sprayed into the pharynx, followed by tracheal intubation. Fentanyl 4 g/kg was administered intravenously at the start of anesthesia, and anesthesia was then maintained with intravenous fentanyl and inhalation of 2-3% sevoflurane. Patients received 25 mL/kg of fluid during the first one hour after the start of infusion. After taking the blood samples for the second measurement, infusion rate was changed to 4 mL/kg/hr. Then the final blood samples were taken 4 hours after the start of infusion for the third measurement. The measurements included the following parameters: 1) blood cell counts (RBC, WBC, Platelet), 2) electrolytes (Na^+, K^+, Mg^{2+}), 3) blood glucose, 4) hormones (insulin, glucagon), 5) lactate, 6) pyruvate, 7) non-esterified fatty acid (FFA), 8) acetoacetic acid, 9) hydroxybutyric acid, and 10) acetone. Blood cell counts were measured using XE-2100 (Sysmex Co., Kobe, Japan), and electrolytes were analyzed using JCA-BM2250 (JEOL LTD., Tokyo, Japan). Blood glucose concentration was measured with the hexokinase UV method. Insulin was measured with enzyme immunoassay and glucagon was measured with radioimmunoassay. Lactate and pyrvate were measured with enzymatic assay with lactate oxidase and pyrvate oxidase, respectively. FFA was measured using enzymatic assay with the use of 3-octenoic acid. Keton bodies were measured with enzymatic cycling assay.

The data are presented as means±SD. Analysis of variance (ANOVA) was used to assess the difference in age, height, weight and urine volume between groups; and chi-square test was used for gender comparison. The group means for each blood sample parameters were determined and compared using ANOVA repeated measures, with post-hoc Tukey-Kramer test for time in each group. A p value less than 0.05 was considered as the level of statistical significance.

RESULTS

There were no significant differences in the demographic background (age, gender, height and weight) of patients between the G/Mg group (n=12) and the C group (n=14); G/Mg group: 9 males and 3 females, 67±8 year-old, 158±7 cm, 61±12 kg, and C group: 9 males and 5 females, 65±7 year-old, 155±9 cm, 56±10 kg. The results of each measurement are shown in table 1 (means ± SD).

In the G/Mg group, all 12 patients underwent spinal surgery for spinal canal stenosis; 4 patients in supine and 8 patients in prone position. Duration of surgery was 245±99 min. The blood loss volume was 162±131 ml and total infusion volume was 2243±461 ml, which contains 14.29±2.94 g of NaCl and 0.46±0.09 g of $MgCl_2$. In the C group, 12 patients underwent spinal surgery, one underwent resection of a tumor in the back and one underwent arthroplasty of the hand; 3 patients in supine and 11 patients in prone position. Duration of surgery was 255±89 min. Volume of blood loss was 203±162 ml and total infusion volume was 2137±363 ml, which contained 12.82±2.18 g of NaCl. There were no significant differences in the duration of surgery and blood loss volume between both groups. No patients received blood transfusion in both groups.

Change in blood cell count (RBC, WBC, platlet)

In both groups, RBC, WBC and platelets decreased at the

Table 1 Alteration of RBC, WBC, platelet, Na^+, K^+, Ca^{2+}, Glucose, Insulin, Glucagon, Lactate, Pyruvic acid.

	G/Mg Group			C Group		
	baseline	1 hour	4hurs	baseline	1 hour	4hurs
RBC	457±109	345±45*	368±45*	447±52	360±41*	375±52*
WBC	5.6±1.0	4.5±1.1**	5.9±1.8$^{\#}$	6.0±1.8	4.7±1.5**	7.3±2.4$^{\#\#}$
Platelet	20.8±5.8	15.9±3.9*	17.2±6.1*	22.3±5.5	17.2±3.6*	17.3±4.2*
Na^+	143.0±2.6	143.1±2.1	143.3±2.8	142.6±2.3	141.8±2.3*	142.3±3.4
K^+	4.27±0.26	3.89±0.19**	4.03±0.25$^{\#}$	4.25±0.34	3.82±0.25**	3.84±0.35**
Ca^{2+}	8.98±0.63	8.07±0.44*	8.13±0.49*	9.09±0.37	8.13±0.39**	8.12±0.38**
Glucose†	95±17	170±19**	119±16$^{*\#\#}$	100±11	94±15	109±9$^{*\#\#}$
Insulin†	4.7±1.9	9.4±6.4	6.4±2.4	3.8±2.1	2.5±4.7**	3.4±2.3$^{\#\#}$
Glucagon	103±36	58±22**	59±17**	90±43	69±32**	69±37**
Lactate	11.3±3.6	17.0±5.9**	19.6±9.1**	13.1±4.4	12.2±2.9	17.0±5.4$^{\#}$
Pyruvate	0.56±0.26	0.98±0.35**	0.81±0.42	0.70±0.19	0.76±0.28	0.87±0.36
FFA†	0.65±0.26	0.43±0.25	0.44±0.22	0.67±0.13	0.50±0.10**	0.79±0.20$^{\#\#}$

Normal range: Insulin (3-15 U/mL), Glucagon (40-140 pg/mL), Lactate (4-16 mg/dL), Pyruvate (0.3-0.9 mg/dL)
FFA (Non-esterified fatty acid: 0.1-0.8 mEq/L)

Data shown as mean±SD. * and ** indicate $p<0.05$ and 0.01 in comparison to base line in the group, and $^{\#}$ and $^{\#\#}$ indicate $p<0.05$ and 0.01 in comparison to 1h values. † indicates $p<0.01$ between groups.

Figure 1

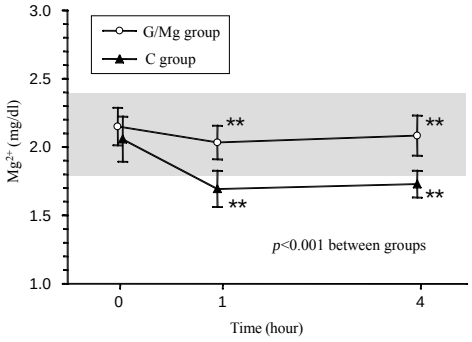

Figure 1. Changes in serum Mg^{2+} before induction of anesthesia, 1 hour and 4 hours after the start of infusion in 12 patients receiving the G/Mg solution (filled triangle) and 14 patients receiving the C solution (open circle). Data expressed as mean±SD.

second measurement, and RBC and platelets decreased further at the third measurement. White blood cells increased significantly to more than the pre-infusion value at the third measurement. There were no significant differences between the groups with regard to RBC, WBC and platelets (Table 1).

Serum electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+})

No significant differences in Na^+, K^+ and Ca^{2+} were found between the study groups (Table 1). Neither did these electrolytes decrease below normal values in any of the measurements.

Mg^{2+} decreased significantly at the second measurement in both groups compared to the pre-infusion value. In the G/Mg group, Mg^{2+} concentrations were maintained within the normal range for all measurements (baseline: 2.15±0.14 mg/dL, 1hour: 2.03±0.12 mg/dL, 4hours: 2.08±0.15 mg/dL). In the C group, on the other hand, Mg^{2+} concentration decreased to below the normal value at the second measurement and this decrease remained at the third measurement (baseline: 2.06±0.17 mg/dL, 1hour: 1.69±0.13 mg/dL, 4hours: 1.73±0.10 mg/dL). Magnesium (Mg^{2+}) concentrations of the C group was significantly lower than that of the G/Mg group (Fig. 1).

Blood and urine glucose

The blood glucose level changed differently between the two groups. In the C group, it remained the same at the second measurement and increased at the third. In the G/Mg group, it increased significantly to 170±19 mg/dL in the second measurement, and decreased at the third, although it remained higher than the pre-infusion value (Table 1).

Urine glucose was not detected, except in one urine sample at the second measurement of one patient in the G/Mg group. Total urine volume for 4 hours were 442±323 mL in the G/Mg group and 378±262 mL in the C group. This difference was not significant.

Insulin and glucagon

The levels of insulin were different between the two groups, while those for glucagons were not. In the G/Mg group, the serum insulin concentration did not change significantly. In the C group, on the other hand, it decreased to below the normal limit at the second measurement, and recovered to within the normal at the third measurement. In both groups, serum glucagon concentrations remained within normal ranges, and there were no significant differences in glucagon levels between the groups (Table 1).

Lactate, pyruvate and FFA

In the G/Mg group, serum lactate increased to above the normal range at the second and third measurements, while it increased only at the third measurement in the C group. In the G/Mg group, serum pyruvate increased to above the normal range at the second measurement, but it returned to normal at the third. In the C group, it tended to increase, but this increase did not reach a significant difference. There were no significant differences between groups with regard to lactate and pyruvate (Table 1).

Significant differences in FFA levels were found between the two groups. The serum FFA decreased significantly in the C group at the second measurement, and increased above the pre-infusion value close to the upper limit at the third, while in the G/Mg group it did not change significantly (Table 1).

Serum ketones

Significant differences in hydroxibutyric acid levels were found between the two groups. In the G/Mg group, serum acetoacetic acid and hydroxibutyric acid stayed in the same level among the three measurements (acetoacetic acid; baseline: 30.7±20.4 μmol/L, 1hour: 25.3±15.0

Figure 2

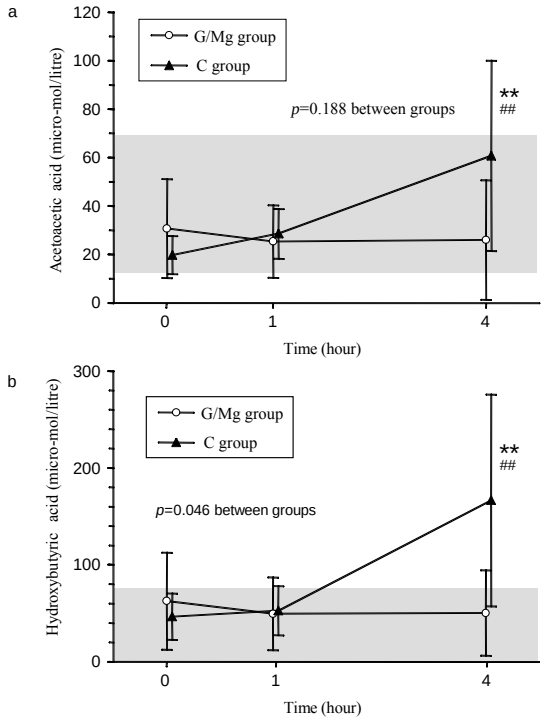

Figure 2. Changes in serum acetoacetic acid (a) and hydroxybutyric acid (b) before induction of anesthesia, 1 hour and 4 hour after the start of infusion in 12 patients receiving the G/Mg solution (filled triangle) and 14 patients receiving the C solution (open circle). Data expressed as mean±SD.

μmol/L, 4hours: 26.0±24.7 μmol/L, hydroxibutyric acid; baseline 62.7±50.2 μmol/L, 1hour 49.5±37.5 μmol/L, 4hours 50.2±43.9 μmol/L) (Fig. 2a, 2b). In the C group, however, acetoacetic acid increased significantly from the first to the second and third measurements (baseline: 19.7±7.8 μmol/L, 1hour: 28.6±10.3 μmol/L, 4hours: 60.7±39.3 μmol/L), and hydroxibutyric acid significantly increased above the upper limit at the third measurement (baseline 46.6±23.8, 1hour: 52.6±25.2 μmol/L, 4hours: 166.5±109.2 μmol/L). Acetone was not detected at any measurements in all patients.

DISCUSSION

In the present study, we aimed to analyze the effect of G/Mg solution infusion during surgery on glucose metabolism and serum Mg^{2+} concentrations. We found that ketogenesis was prevented and serum Mg^{2+} maintained.

To maintain basal metabolism and not increase catabolism, glucose could be administered during the perioperative period. It has been reported that carbohydrate-rich fluids given orally before anesthesia alters metabolism and reduces the catabolic response in the perioperative period, and is useful for postoperative recovery (6). However, it is often difficult to give appropriate dose of carbohydrate to elderly patients before surgery. In the current study, oral intake including drinking was stopped for 12 hours before anesthesia to regulate water intake in all patients. Therefore, 25 ml/kg of acetated Ringer solution was administered rapidly for the first 1 hour to compensate for the long fasting period.

Infusion of 5% glucose solution during anesthesia and surgery is not in clinical routine presently, due to increased risk of hyperglycemia that is deleterious to many organs (8,9). By choosing the G/Mg solution, however, serum glucose concentration never exceeded 200 mg/dL even after rapid infusion for one hour, and it returned close to the baseline (table 1). No hypoglycemia was observed in the G/Mg group while serum glucose decreased below 70 mg/dL in two of 14 patients of the C group at the second measurement. In the G/Mg group, patients received 2243±461 ml of infusion, including 22.43±4.61 g of glucose (89.7±18.4 kcal) for 4 hours during the study period. On the other hand, the basal energy expenditure of 12 patients of the G/Mg group was calculated at 1250±172 kcal/day (52.1±7.2 kcal/hr) with the Harris-Benedict equation (14). The total calorie content given for 4 hours compensates for 43% of basal energy expenditure.

Lactate and pyruvate are yielded from glucose. In the G/Mg group, serum lactate and pyruvate significantly increased at the second measurement, probably reflecting the increase in exogenous glucose metabolism. Such increase was not observed at the second measurement in the C group. In the C group, acetoacetic and hydroxybutyric acids increased significantly at the third measurement and non-esterified fatty acid also increased at the third measurement (Fig. 2). These results strongly suggest that no supplementation of glucose during surgery causes an increase in glyconeogenesis and a decrease of glycogenolysis due to the decrease of glycogen in patients. In addition, increase of lactate and pyruvate at the third measurement in the C group might reflect increase of metabolism of endogenous glucose produced by glyconeogenesis. Our study did not include extremely long surgery, and patients were examined three times only up to 4 hours, yet obvious ketogenesises were recognized. Therefore, in longer cases, no supplementation of glucose may result in even more severe metabolic acidosis.

Magnesium works as a cofactor that is required for the energy-dependent membrane pumps controlling electrolyte gradients (11,12) and as a natural Ca^{2+} channel blocker, thereby modulating cardiac and vascular smooth muscle contraction (15,16). In addition, magnesium has a direct effect on calcium uptake in bronchial smooth muscle, resulting in a significant bronchodilatory effect (17). Therefore, potential hypomagnesemia should be avoided during perioperative period. However, serum concentration of Mg^{2+} often decreases during surgery, since a large amount of infusion dilute serum Mg^{2+} concentrations. Further, no supplementation of glucose increases gluconeogenesis, leading to an increase in non-esterified fatty acid, which chelates Mg^{2+} and reduces serum Mg^{2+} concentrations (18). In our results, the serum Mg^{2+} concentration of the C group decreased below the normal limit at the second measurement, and this hypomagnesemia did not improve at the third measurement (Fig. 1). Presently, serum Mg^{2+} concentration is usually not examined during surgery although many kinds of solutions are used for surgery.

In conclusion, total glucose infused in this study compensated 43% of basal energy expenditure, and prevented ketogenesis effectively. In addition, the G/Mg solution maintained normal serum Mg^{2+} concentration.

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AUTHOR DISCLOSURES

Takeshi Yokoyama, Kunio Suwa, Fumiyasu Yamasaki, Reiko Yokoyama, Koichi Yamashita, Eva Selldén, no conflicts of interest.

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Original Article

Intraoperative infusion of acetated Ringer solution containing glucose and ionized magnesium reduces ketogenesis and maintains serum magnesium

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手術期間灌輸含葡萄糖及游離鎂的醋酸格林溶液降低生酮作用及維持血清鎂

手術期間葡萄糖灌輸對葡萄糖代謝的影響並未透徹研究。本研究檢測手術期間灌輸含 1%葡萄糖及游離鎂的醋酸格林溶液對生酮作用及血清鎂濃度的影響。歸類為 ASA I-II 的病人(年齡 51-80 歲)隨機分組接受醋酸格林溶液灌輸。G/Mg 組接受含 1%葡萄糖、140 meq/L 鈉離子及 2 meq/L 鎂離子，C 組接受 130 meq/L 鈉離子但不含葡萄糖及鎂的溶液。兩種溶液在第一小時都是以 25 mL/Kg 速度灌注，隨後維持每小時 4 mL/Kg。收集 3 次血液樣本：灌注前、灌注開始 1 小時及 4 小時各一次。分析每個樣本的電解質及葡萄糖代謝。快速灌注後，G/Mg 組病人的血糖值顯著上升至 170±19 mg/dL，但 4 小時後即回到基礎值，而血清酮體並未增加。反之，C 組病人的血糖值從未超過 110 mg/dL，但在第 3 測量點的酮酸-乙醯乙酸及氫氧化丁酸濃度都顯著升高。

關鍵字：手術間灌輸、葡萄糖代謝、酮酸中毒、胰島素、鎂