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Effects of Exogenous Intravenous Glucose on Plasma Glucose and Lipid Homeostasis in Anesthetized Children

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Whether or not intravenous glucose administration during pediatric anesthesia is necessary remains a controversial issue. The current study was designed to investigate the effect of glucose infusion on concentrations of plasma glucose, nonesterified fatty acids (NEFA), triglycerides, ketone bodies, and insulin and to determine whether the use of solutions containing less than 5% glucose would maintain physiologic plasma glucose concentrations during tympanoplasty lasting about 6 h. Forty-five children aged between 1.5 and 9 yr were divided randomly into three groups of 15 patients each to receive the following intravenous solutions: LR group, lactated Ringer's solution (LR) alone; D2LR group, 2% glucose in LR; and D5LR group, 5% glucose in LR. All fluids were infused at a rate of 6 ml · kg^{-1} · h^{-1} until 1 h after anesthesia. In the LR group, the plasma glucose concentrations remained unchanged perioperatively compared with basal values, whereas in the D2LR group they showed a gradual increase during surgery but remained normoglycemic. On the other hand, in the D5LR group, the plasma glucose concentrations increased markedly both during and after the operation. Furthermore, 3 of 15 patients showed hyperglycemia of more than 300 mg · dl^{-1} during anesthesia. There was no evidence of lipid mobilization or impaired secretion of insulin, since plasma NEFA, triglycerides, ketone bodies, and insulin remained within normal concentration ranges throughout the sample period in the three groups. These data indicate the possibility that even in uncomplicated pediatric surgery of long duration, intravenous infusion of glucose at a concentration of 2% and less may be sufficient to maintain plasma glucose concentrations within physiologic ranges and to prevent compensatory increase in lipid mobilization (lipolysis) when fluids are infused at a rate of 6 ml · kg^{-1} · h^{-1}. Extrapolation of the results to the general population is limited because of the small number of patients and the limited age range studied. (Key words: Anesthesia: pediatric. Metabolism: glucose; free fatty acid; ketone bodies; triglycerides. Hormone: insulin.)

ANESTHESIOLOGISTS HAVE FOCUSED considerable interest on perioperative fluid management by which appropriate blood glucose concentrations in children are maintained. Although many reports concerning perioperative blood concentrations of glucose in healthy pediatric patients have been published,[1–8] the necessity of intravenous glucose administration during pediatric anesthesia remains a controversial issue. Some investigators have documented that most children have normal levels of blood glucose despite preoperative fasting and respond to anesthesia and surgery with an increase in blood glucose.[8] There is a danger of hyperglycemia, as well as of hypoglycemia; compared with normoglycemia, hyperglycemia associated with cerebral hypoxia results in accumulation of lactate in the brain.[9] This has been described as an important risk factor in the production of neurologic damage. Furthermore, hyperglycemia causes osmotic diuresis, which may influence circulating blood volume, especially in small infants. Thus, it has been suggested that glucose-free solutions be used during surgery.[8]

Despite this hyperglycemic response, the possibility that hypoglycemia may remain undetected during anesthesia has led many authors to recommend the routine use of glucose-containing solutions for perioperative fluid management.[2,3,10]

All of those investigators,[1–8,10] however, studied pediatric anesthesia of relatively short duration. We undertook the current study to investigate the effect of glucose infusion on plasma concentrations of glucose, insulin, nonesterified fatty acids (NEFA), triglycerides, and ketone bodies in pediatric anesthesia lasting more than 6 h, and to determine whether the use of solutions containing less than 5% glucose (a glucose infusion rate of less than 0.3 g · kg^{-1} · h^{-1}) would maintain physiologic plasma glucose concentrations without inducing hyper- or hypoglycemia even during minor surgical procedures.

Materials and Methods

SUBJECTS

The protocol for the study was approved by the Human Investigation Committee of Kobe University School of Medicine, and informed consent was obtained from the parents of all patients.

Plasma concentrations of glucose, insulin, ketone bodies, triglycerides, and NEFA were determined in 45 children (ASA physical status 1) ranging in age from 1.5 to 9 yr. Children with neurologic, cardiac, endocrine, or metabolic disease were excluded. They were randomly divided into three groups of 15 patients each according to glucose concentrations infused, as follows: LR group, lactated Ringer's solution (LR) alone as a control; D2LR group, LR containing 2% glucose; and D5LR group, LR containing 5% glucose. All fluids were infused at a rate

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of 6 ml · kg^{-1} · h^{-1} until 1 h after anesthesia, when patients were in the intensive care unit, such that glucose infusion rates in LR, D2LR, and D5LR were 0, 0.12, and 0.30 g · kg^{-1} · h^{-1}, respectively. The two glucose-containing solutions were prepared in the hospital pharmacy. All of the patients underwent elective tympanoplasty with minimal blood loss.

Anesthesia

Induction of anesthesia in all cases was started at 8:30 AM. The standard preoperative instruction to parents was not to allow children any solid food after midnight. All patients fasted for 4–6 h before operation, according to age. The last oral intake prior to anesthesia was 10 ml · kg^{-1} 5% glucose dissolved in water. Preanesthetic medication consisted of diazepam 0.3 mg · kg^{-1} by mouth 1 h and atropine 0.02 mg · kg^{-1} intramuscularly 30 min before induction of anesthesia. Anesthesia was induced with nitrous oxide 4 l · min^{-1}, oxygen 2 l · min^{-1}, and halothane in gradually increasing concentrations up to 2.5%. Immediately after onset of sleep in all patients, infusion was started and tracheal intubation was facilitated by pancuronium bromide 0.1 mg kg^{-1} intravenously. Halothane was discontinued following tracheal intubation, and anesthesia was maintained with 1–1.5% enflurane and 60% nitrous oxide in 40% oxygen. Muscle relaxation was obtained by intermittent administration of pancuronium. No patient received blood during the study. Using a rectal probe, body temperature was maintained between 37.0–37.5° C to avoid stress from hypothermia. Following surgery, trachea was extubated in the operating room after residual neuromuscular blockade had been antagonized with neostigmine 0.05 mg · kg^{-1} and atropine 0.02 mg · kg^{-1}. Apart from anesthetics, muscle relaxant and neuromuscular antagonist, no drugs, including vasoactive drugs, were administered to any patient. Each concentration of glucose infusion was continued until 1 h after completion of anesthesia. Mean (±standard error of the mean) urine output in the LR, D2LR, and D5LR groups were 1.6 ± 0.1, 1.6 ± 0.1, and 1.7 ± 0.2 ml · kg^{-1} · h^{-1}, respectively, and there were no differences between groups. The volume was accepted as within standard values in pediatric anesthesia, suggesting that the infusion rate performed in the current study (6 ml · kg^{-1} · h^{-1}) was not excessively great. In all patients, the postoperative course was uneventful.

Measurements

In order to obtain blood samples for determining plasma concentrations of glucose, insulin, ketone bodies, triglycerides, and NEFA and to monitor blood pressure (BP), a catheter was inserted into the radial artery immediately following the disappearance the eyelash reflex. The first blood sample was taken prior to the intravenous infusion of any fluid. The timing of the blood sample collections is shown in figure 1. All blood samples were centrifuged within 10 min of collection, and serum was separated and stored at −70° C until analyzed. Plasma glucose concentrations were estimated using a hexokinase method.[11] Although the hexokinase method is precise, the results are not immediately available. Therefore, blood glucose determinations were performed throughout the study also using reflectance meter techniques (Glucometer®, Ames, Elkhart, IN). The results from this instrument were available immediately, such that we could check whether or not severe hypoglycemia or hyperglycemia had occurred in any patient. Hypoglycemia was defined as a plasma glucose concentration of less than 50

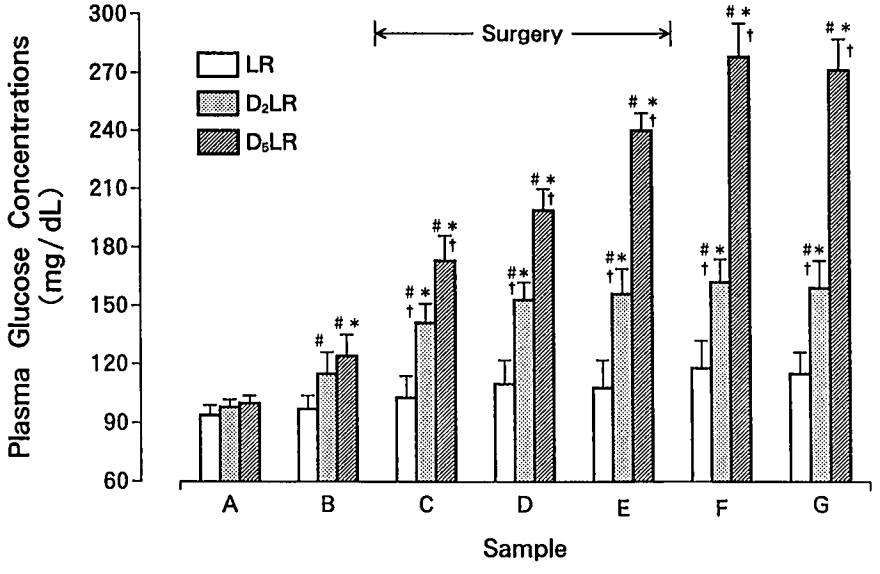

FIG. 1. Plasma glucose concentrations (mean ± SEM) for three groups of patients. Blood sampling times: *A:* at induction of anesthesia (immediately before the start of infusion of glucose-containing or glucose-free solution); *B:* immediately before the start of operation (approximately 30 min after induction of anesthesia); *C:* 1 h after induction of anesthesia; *D:* 3 h after induction of anesthesia; *E:* 5 h after induction of anesthesia; *F:* immediately after completion of anesthesia; and *G:* 1 h after completion of anesthesia. Open columns = LR group as a control; dotted columns = D_2LR group; and striped columns = D_5LR group. #$P < 0.05$ *versus* basal values (*A*) within groups; *$P < 0.05$ *versus* control (LR group); †$P < 0.05$ for D_2LR group *versus* D_5LR group.

$mg \cdot dl^{-1}$,[12] and hyperglycemia as greater than 200 $mg \cdot dl^{-1}$.[13] Plasma insulin concentrations were quantified in duplicate, using commercial radioimmunoassay kits supplied by Dainabot (Tokyo, Japan). The intra- and interassay coefficients of variance were 4.1 and 5.2%, respectively. Plasma concentrations of NEFA and total ketone bodies were measured according to the method of Itaya and Ui[11] and Harano *et al.*,[14] respectively. Commercial enzymatic assay kits (Eiken-Hitachi Test TG555®, Eiken, Tokyo, Japan) were used to determine plasma triglyceride concentrations.

Arterial blood gas (*p*H, carbon dioxide tension, oxygen tension, and base excess) were measured at each point of sample collection using an ABL3® analyzer (Radiometer, Copenhagen, Denmark), as were blood concentrations of potassium and sodium, using a KNA1® analyzer (Radiometer). The results of all of these analyses were consistently within normal ranges throughout the study.

During surgery, systolic and diastolic BP were maintained within the physiologic ranges of 90–119 mmHg and 52–79 mmHg, respectively. Heart rate was maintained between 81 and 120 beats per min, indicating no evidence of persistent sympathetic response. No ventricular arrhythmias were observed throughout the study.

Statistics

Statistical analysis was performed using analysis of variance for repeated measurements and Bonferroni correction for multiple comparison. $P < 0.05$ was deemed significant.

Results

Mean (±SEM) age, weight, anesthesia and operation time, length of preoperative fasting period, and bleeding volume in the three groups were 4.6 ± 0.6 yr, 18 ± 1.9 kg, 6.8 ± 0.2 h, 6.1 ± 0.2 h, 5.3 ± 0.3 h, and 80 ± 16 ml, respectively, and did not differ among the groups. There was no difference in plasma glucose concentrations at induction of anesthesia among the three groups (fig. 1). No patients were found to be hypoglycemic at this time. Times from induction of anesthesia to the start of surgery were 29 ± 1.6, 31 ± 1.7, and 31 ± 1.5 min (mean ± SEM) in the LR group, D2LR group, and D5LR group, respectively.

In the LR group, mean plasma glucose concentrations remained unchanged throughout the study, compared with basal values at induction of anesthesia. In the D2LR and D5LR groups, plasma glucose concentrations continued to increase during anesthesia and reached maximum values (168 $mg \cdot dl^{-1}$ and 271 $mg \cdot dl^{-1}$ in the D2LR and D5LR groups, respectively) immediately after completion of anesthesia. Mean plasma glucose concentrations remained markedly increased in the D5LR group 1 h after completion of anesthesia. Compared with the LR group (control), plasma glucose concentrations in the D2LR and D5LR groups were higher during and after operation. The magnitude of the increase in plasma glucose concentrations was greater in the D5LR group than in the D2LR group. The intraanesthetic changes in plasma glucose concentrations (differences in plasma glucose concentrations between 1 h after anesthesia and at induction) are shown in table 1. Although three patients in the LR group showed a decrease in plasma glucose concentration 1 h after anesthesia compared with the concentration at induction (basal values), no patients became hypoglycemic. Plasma glucose concentrations in all patients in the D2LR and D5LR groups increased during surgery.

Figure 2 shows that plasma concentrations of NEFA, total ketone bodies, and triglycerides remained within normal ranges throughout the study in the three groups, suggesting that lipid mobilization did not occur. There were no significant intergroup differences in any parameters. Figure 3 demonstrates that although plasma insulin concentrations in the three groups gradually increased

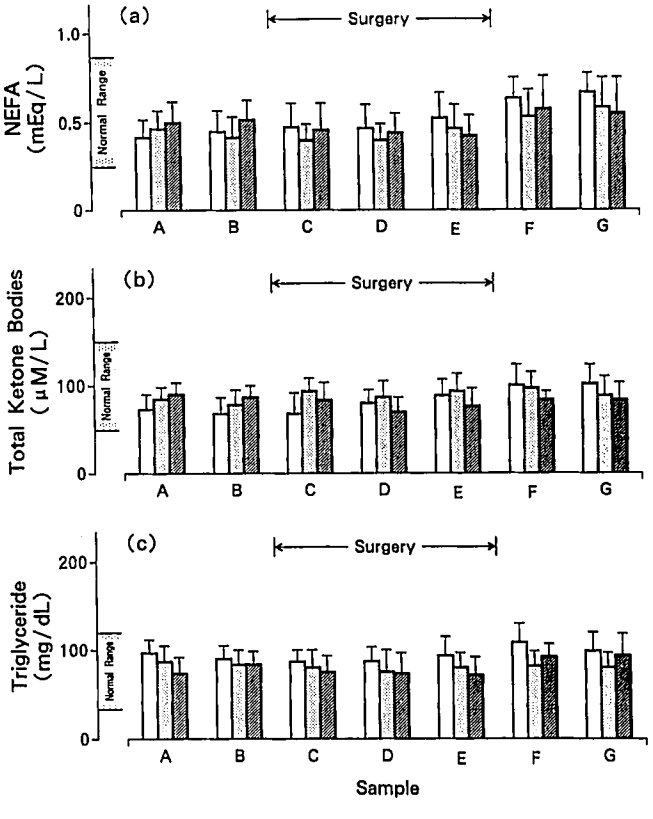

FIG. 2. Plasma nonesterified fatty acids (NEFA), total ketone bodies, and triglycerides concentrations (mean ± SEM) for the three groups of patients. *a:* NEFA; *b:* total ketone bodies; *c:* triglycerides. Blood sampling times are as in Figure 1. Open columns = LR group as a control; dotted columns = D_2LR group; striped columns = D_5LR group. There was no significant difference among the three groups throughout the study.

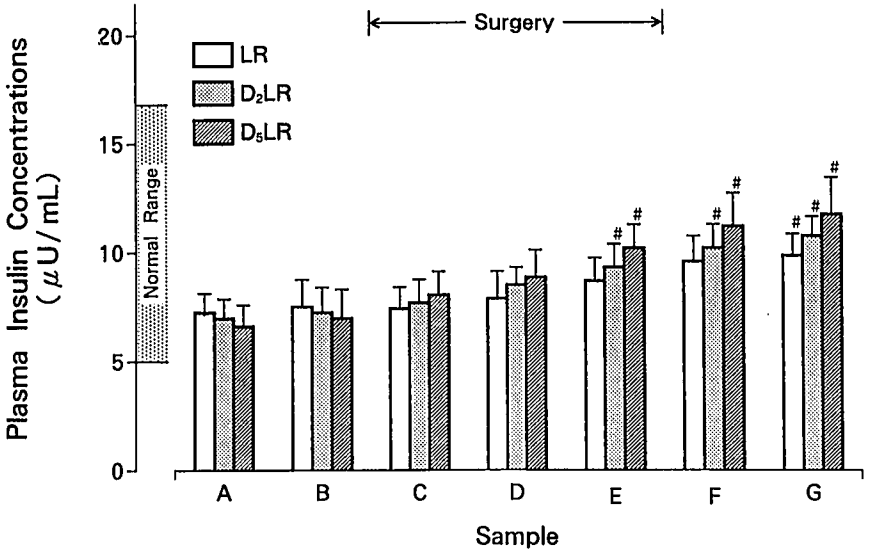

FIG. 3. Plasma insulin concentrations (mean ± SEM) for the three groups of patients. Blood sampling times are as in Figure 1. Open columns = LR group as a control; dotted columns = D_2LR group; striped columns = D_5LR group. There was no significant difference among the three groups throughout the study. #$P < 0.05$ *versus* basal values (*A*) within groups.

during anesthesia, the intergroup difference was not significant at any point.

Discussion

In adult patients, surgical stress itself has been shown to increase blood glucose concentrations without a concomitant increase in plasma insulin concentrations.[15,16] In the current study, all children receiving glucose-containing solutions intraoperatively responded with an increase in plasma glucose concentrations as anticipated, while in three patients receiving glucose-free solutions (the LR group), plasma glucose concentrations did not increase. However, the finding that most children receiving glucose-free intravenous fluid solutions demonstrated an increase in their plasma glucose concentrations also was expected and confirmed previous findings.[4]

The hyperglycemic response to glucose infusion during surgery and anesthesia is attributable to a decrease in glucose tolerance believed to be induced by any of the following mechanisms[8,17]: 1) impaired insulin secretion; 2) decreased biologic response of tissues to insulin, such as a diminished peripheral glucose utilization; 3) increased gluconeogenesis and/or glycogenolysis; 4) an increased hepatic glucose output and/or splanchnic release of glucose as a consequence of the increased catabolic processes; and 5) increased peripheral uptake of gluconeogenic substances. It is well established that various hormones released by surgical stress play a crucial role in reducing glucose tolerance during perioperative periods.[18] The release of cortisol, adrenaline, or glucagon inhibits the release of insulin and triggers a cascade of metabolic changes in the direction of catabolism, which results in the hyperglycemia observed during and after surgery.[19,20] These findings have led some authors to conclude that glucose-containing solutions may not be necessary to maintain adequate glucose concentrations in healthy pediatric patients during surgery. Although in the current study, plasma concentrations of catecholamines and cortisol were not determined, the combination of surgery and anesthesia, regardless of inhalation anesthetics, has been shown to increase their concentrations.[21–24] The results of the LR group may be attributed to the probable increases in catecholamines and cortisol during surgery, although in minor surgery such as tympanoplasty, the increases are believed to be less marked than in major surgery.

On the other hand, it is well documented that an extensive lack of glucose supply enhances lipolysis, thereby leading to ketogenesis.[2,3,25] To prevent lipolysis, glucose-containing solutions are recommended almost invariably as a perioperative fluid for pediatric surgery. Although no group in this study contained many children aged 4–7 yr, who have a tendency regardless of surgery to develop ketotic hypoglycemia, plasma NEFA concentrations in the group receiving the glucose-free solution seemed to increase, though not significantly. This study has shown that contrary to general accepted opinion, children may

TABLE 1. Intraanesthetic Increase of Plasma Glucose Concentrations (mg/dl)

Intraanesthetic Change in Plasma Glucose Concentrations	Groups		
	LR	D2LR	D5LR
Mean ± SEM	20 ± 5.1	64 ± 5.3	171 ± 7.5
Range	−16–48	34–99	112–213

LR = lactated Ringer's solution (LR) alone; D2LR = LR containing 2% glucose; D5LR = LR containing 5% glucose.

maintain normoglycemia during minor surgery of long duration without exogenous glucose administration.

In the current study, there was no difference in plasma insulin concentrations, which increased gradually in each group during surgery. In patients receiving D5LR, insulin release did occur but did not attenuate the increase in blood glucose concentrations. The mechanism for this is unknown. These observations are in contrast to those of Äärimaa *et al.*,[26] who reported a suppression in insulin secretion 4–5 h after the initiation of surgery in adults who were given a constant glucose infusion. This suppression may be due to the action of epinephrine, which competes with glucose for the glucose receptors, leading to insensitivity of the pancreas to glucose.[27] Many anesthetic agents themselves have no influence on blood glucose and plasma insulin levels.[28,29]

The question of whether preoperative fasting causes hypoglycemia in healthy children has not been resolved.[1–8] The current study has shown the ability of healthy children aged 1.5–9 yr undergoing minor surgical procedures to maintain glucose homeostasis after a short period of fasting, only 4–6 h. We emphasize that our results are applicable only to patients who are fasting for a relatively brief time. Fasting periods of even shorter duration probably would further reduce the need for glucose infusions and the risk of hypoglycemia. Recent work has demonstrated that children may tolerate a considerable period of fasting (range 2.5–21 h) without evidence of hypoglycemia.[30,31]

In conclusion, the current study demonstrated that neither hypoglycemic nor lipolytic responses (lipid mobilization) were observed during infusions of solutions containing 2% glucose or less when fluids were infused at a rate of 6 $ml \cdot kg^{-1} \cdot h^{-1}$. Even in minor surgery producing less severe stress and lasting a long period of time, glucose infusion at a rate of less than 0.12 $g \cdot kg^{-1} \cdot h^{-1}$ may be sufficient to maintain appropriate plasma glucose concentrations and to prevent compensatory increase in lipid mobilization in otherwise healthy children. However, we emphasize that these results, because of the small number of patients studied, cannot be extrapolated either to neonates or to infants, who might have a greater need for glucose, or to the general population. Further investigations are required for such evaluation.

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