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

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Background: Whether intravenous glucose administration to infants during anesthesia is necessary remains to be elucidated. The current study was designed to investigate the effect of exogenous glucose infusion on plasma glucose and lipid homeostasis in infants undergoing minor surgery.

Methods: Sixty infants (inpatients, ASA physical status I) between 1 and 11 months of age were divided randomly into three groups as follows: LR group, lactated Ringer’s solution (LR) alone; D2LR group, 2% glucose in LR; and D5LR group, 5% glucose in LR. Anesthesia was induced and maintained with halothane and nitrous oxide in oxygen. All fluids were infused at a rate of 6 ml·kg⁻¹·h⁻¹ until 1 h after surgery. Plasma concentrations of glucose, nonesterified fatty acids, ketone bodies, insulin, and cortisol were determined at induction of anesthesia, at the end of surgery, and 1 h after surgery.

Results: No infants in the three groups had hypoglycemia (<50 mg·dl⁻¹) throughout the study. In the LR group, plasma glucose concentration remained unchanged perioperatively compared with the basal values (at induction), whereas in the D2LR group, it increased during surgery but remained normoglycemic. In the D5LR group, plasma glucose concentration increased markedly both during and after surgery. In 6 of 20 infants, plasma glucose was greater than 200 mg·dl⁻¹ at the end of surgery. In 8 of 20 infants receiving glucose-free infusion, plasma glucose concentrations decreased at the end of surgery. In contrast, the plasma glucose concentration increased in infants receiving glucose infusion. In the LR group, plasma concentrations of nonesterified fatty acids and ketone bodies increased at the end of and after surgery, suggesting lipid mobilization. The base excess decreased in the LR groups as concentration of the ketone bodies increased. Plasma insulin concentrations increased in the D2LR and D5LR groups and decreased after surgery in infants receiving a glucose-free solution. No intergroup differences in plasma cortisol concentrations existed at any sample point.

Conclusions: These data indicate that, in otherwise healthy infants undergoing minor surgery, intravenous infusion of 2% glucose may be sufficient to maintain plasma glucose concentrations within physiologic ranges and to prevent a compensatory increase in lipid mobilization. When fluids are infused at a rate of 6 ml·kg⁻¹·h⁻¹, there are limitations in extrapolating the results to neonates. (Key words: Anesthesia. Hormone; cortisole; insulin. Metabolism: free fatty acid; glucose, ketone bodies.)

The necessity of intravenous glucose administration during pediatric anesthesia remains a controversial issue. Many reports concern perioperative blood concentrations of glucose in healthy pediatric patients that have been published. We previously reported that infusions of solutions containing 2% glucose or less may be sufficient to maintain appropriate plasma glucose concentrations and to prevent a compensatory increase in lipid mobilization in otherwise healthy children when fluids were infused at a rate of 6 ml·kg⁻¹·h⁻¹. However, limited data are available concerning the intraoperative necessity of glucose infusion in infants who might have a greater need for exogenous glucose per kilogram of body weight.

We conducted the current study to investigate the effect of exogenous glucose infusion on plasma glucose and lipid homeostasis in infants undergoing minor surgery and to determine the appropriate concentration of glucose solution used for such a population to maintain physiologic plasma glucose concentrations during surgery.

Materials and Methods

Subjects
After obtaining institutional approval and informed consent from the parents of all children, we determined...
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plasma concentrations of glucose, insulin, ketone bodies, nonesterified fatty acids (NEFA), and cortisol in 60 otherwise healthy infants (inpatients ASA physical status 1) ranging in age from 1 to 11 months. They were divided into three groups of 20 patients each randomly using the envelope method according to glucose concentrations infused as follows: LR group, lactated Ringer's solution (LR) alone; D2LR group, LR containing 2% glucose; and D5LR group, LR containing 5% glucose. All fluids were infused at a rate of 6 ml · kg⁻¹ · h⁻¹ until 1 h after anesthesia, when the patients were in the wards. All of the patients underwent elective ophthalmologic surgery or repair of inguinal hernia or hydrocele with minimal blood loss (table 1).

Anesthesia

Induction of anesthesia in all cases began at 8:30 AM. The standard preoperative instruction to parents was to not allow infants 5 months of age or older any milk and solids after midnight. Infants 4 months of age or younger were allowed to ingest breast milk or formula until 6 h before surgery. The last oral intake in both age groups was 10–15 ml · kg⁻¹ · 5% glucose, dissolved in water 3 h before anesthesia. No preanesthetic medication was administered. Anesthesia was induced with 4 l/min N₂O, 2 l/min O₂, and halothane in gradually increasing concentrations up to 1.5%. The first blood sample was collected immediately after we confirmed the loss of consciousness of the infants. The assigned infusion was started and 0.01 mg · kg⁻¹ · h⁻¹ atropine was intravenously administered. Tracheal intubation was facilitated by 0.1 mg · kg⁻¹ intravenous vecuronium bromide. Anesthesia was maintained with 1.0–1.5% halothane and 60% N₂O in oxygen. Muscle relaxation was supplemented with intermittent administration of vecuronium as needed. No patient received blood throughout the study. Body temperature was maintained between 37.1°C and 37.6°C using a rectal probe. After surgery, the trachea was extubated in the operating room after residual neuromuscular blockade had been antagonized with 0.05 mg · kg⁻¹ neostigmine and 0.02 mg · kg⁻¹ atropine. Apart from anesthetics, muscle relaxant, and neuromuscular relaxant antagonist, no drugs, including vasoactive agents, were administered to any patient. In all infants, the postoperative course was uneventful.

Measurements

To obtain blood samples for blood gas analysis and to determine plasma concentrations of glucose, insulin, ketone bodies, NEFA, and cortisol, a catheter was inserted into the radial artery immediately after the disappearance of the eyelash reflex. The first blood sample was taken before the intravenous infusion of any fluid, and subsequent blood samples were collected at the end of surgery and 1 h after surgery. All blood samples were centrifuged within 10 min of collection, and the serum was separated and stored at −70°C until analyzed. Plasma glucose concentrations were estimated using a hexokinase method. Although the hexokinase method is extremely precise, the results are not immediately available. Therefore, another method of blood glucose determination was employed throughout the study using reflectance meter techniques. Glucometer (Ames, Elkhart, IN). With this instrument, the results were yielded immediately, so that we could check whether severe hypoglycemia or hyperglycemia had occurred in any patient. Hypoglycemia was defined as a plasma glucose concentration of less than 50 mg · dl⁻¹,¹¹ and hyperglycemia, greater than 200 mg · dl⁻¹.¹² Plasma concentrations of NEFA and total ketone bodies were measured according to the method of Itaya and Ui¹³ and Harano et al.,¹⁴ respectively. Plasma insulin and cortisol concentrations were quantified in duplicate, using commercial radioimmunoassay kits supplied by Dainabot (Insulin-Riabead, Tokyo, Japan) and Baxter (Gamma-Coat Cortisol, Deerfield, IL), respectively. The intra- and interassay coefficients

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

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of variance were, respectively, 4.6% and 5.6% for insulin and 4.2% and 4.9% for cortisol.

The results of arterial blood gas analyses (pH, P_{\text{CO}_2}, P_{\text{O}_2}, \text{and base excess}) at each point of sample collection using an ABL5 analyzer (Radiometer, Copenhagen, Denmark) as well as blood concentrations of potassium and sodium measured using a KNA1 analyzer (Radiometer) were consistently within normal ranges throughout the study.

During surgery, systolic and diastolic blood pressures were maintained within the physiologic ranges of 71–105 mmHg and 43–68 mmHg, respectively. Heart rate was maintained between 92 and 143 beats/min. No ventricular arrhythmias were observed throughout the study.

Statistics
Statistical analysis was performed using analysis of variance for repeated measures and Bonferroni corrected t tests. Differences with $P < 0.05$ were considered significant.

Results
As shown in table 1, there were no differences in age, weight, anesthesia and operation time, clear fluid volume of the last oral intake, and types of operation among the three groups.

Plasma Glucose Homeostasis
No infants were found to be hypoglycemic throughout the study. There was no difference in plasma glucose concentrations at induction of anesthesia among the three groups (fig. 1). In the LR group, the mean plasma glucose concentrations remained unchanged throughout the study compared with the basal value at induction of anesthesia. In the D2LR and D5LR groups, the mean plasma glucose concentrations continued to increase during anesthesia and reached maximum values (146 and 216 mg·dl\(^{-1}\)) in the D2LR and D5LR groups, respectively 1 h after surgery (at the discontinuation of glucose infusion). Compared with the LR group, plasma glucose concentrations were greater at the end of and after surgery in the D2LR and D5LR groups. The magnitude of the increase in plasma glucose concentrations was greater in the D5LR group than in the D2LR group. In eight infants in the LR group, plasma glucose concentration decreased at the end of surgery compared with that at induction (basal values).

In contrast, plasma glucose concentrations in all patients in the D2LR and D5LR groups increased during surgery. No infants in the D2LR group and six patients receiving 5% glucose infusion became hyperglycemic (>200 mg·dl\(^{-1}\)) at the end of surgery. These proportions of infants having hyperglycemia were significantly different.

Assessment of Lipid Mobilization
Plasma concentrations of total ketone bodies and NEFA remained within normal ranges throughout the study in the D2LR and D5LR groups (fig. 2), suggesting that lipid mobilization did not occur. In contrast, plasma concentrations of total ketone bodies and NEFA in the LR group markedly increased at the end of surgery and thereafter continued to increase.

Plasma Hormone Concentrations
Plasma insulin concentrations in the LR group remained unchanged during surgery but slightly decreased after surgery. In the D2LR and D5LR groups, plasma insulin concentrations gradually increased in association with infusion of glucose and were significantly greater than that in the LR group at the end of surgery and 1 h after surgery (fig. 3). As shown in figure 4, no differences were observed among the three groups in plasma cortisol concentrations.

Blood Gas Analysis (Acid-Base Balance)
Base excess and pH decreased in the LR group compared with the basal value (induction of anesthesia).
Fig. 2. Plasma concentrations of total ketone bodies and non-esterified fatty acids (NEFA; mean ± SD) for the three groups of infants. (A) Total ketone bodies. (B) NEFA. Normal ranges 50–150 μmol/l for ketone bodies and 0.25–0.9 mEq/l for NEFA. *P < 0.05 versus basal values (at induction) within groups. #P < 0.05 versus LR group.

whereas it did not change in the D2LR and D5LR groups (fig. 5).

Discussion

Attention of anesthesiologists has been focused on dangers of hyperglycemia and hypoglycemia associated

Fig. 3. Plasma insulin concentrations (mean ± SD) for the three groups of infants. Normal ranges 5–17 μU/ml. *P < 0.05 versus basal values (at induction) within groups. #P < 0.05 versus LR group.

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with pediatric surgery. Compared with normoglycemia, hyperglycemia associated with cerebral hypoxia results in accumulation of lactate in the brain. This has been described as an important risk factor for production of neurologic damage. Furthermore, hyperglycemia causes osmotic diuresis, which may influence circulating blood volume, especially in infants. Thus, it has been suggested that glucose-free solutions be used during surgery in the current study, plasma glucose concentrations markedly increased in the D5LR group compared with the other two groups: 30% of infants in the D5LR group had hyperglycemia at the end of surgery.

In adult patients, surgery has been shown to increase blood glucose concentrations despite the use of glucose-free solutions during surgery. Some investigators have demonstrated that most children also respond to surgery with an increase in blood glucose. In the previous study, we confirmed this. Otherwise healthy children receiving glucose-free solution or 2% glucose did not become hypoglycemic perioperatively. Furthermore, lipid mobilization for maintenance of physiologic plasma glucose concentrations was not observed in these patients. However, in the current study, plasma glucose concentrations decreased in 40% of infants receiving glucose-free solution, and lipolysis occurred in most infants in this group. These findings may be explained by the fact that, although glycogen stores are likely to be sufficient to prevent lipolysis in otherwise healthy children during prolonged surgery (6 h), infants had insufficient glycogen to prevent lipid mobilization even during surgery of shorter duration (1.5 h).

It is well known that an extensive lack of glucose supply enhances lipolysis leading to ketogenesis. This lack of glucose supply added to low glycogen stores probably is responsible for lipid mobilization to maintain normoglycemia in the LR group, as implicated by the increase in plasma ketone bodies and NEFA concentrations. To prevent lipolysis, therefore, glucose-containing solutions are recommended almost invariably as a perioperative fluid for pediatric surgery. In the current study, ketogenesis did not occur in the glucose-infusion groups. The decrease in base excess accompanied the increase in concentrations of ketone bodies in the LR group. The pH decreased in the LR group as the base excess of the blood may contribute to the decrease in base excess and pH in infants during anesthesia. However, the decrease in these two variables seems to be so small as to have clinical implication. Administration of fluids containing glucose prevented progress of acidosis, probably due to suppression of ketogenesis.

Cortisol has been shown to inhibit the release of insulin and trigger a cascade of catabolic changes, which result in the hyperglycemia during and after surgery. The increase in plasma cortisol concentrations during surgery failed to inhibit insulin release and to increase plasma glucose concentrations in the LR group. On the other hand, consistent with our previous findings in children, insulin release occurred in the glucose-infusion groups but failed to attenuate the increase in plasma glucose concentrations. Although the precise mechanisms for these phenomena are unknown, the duration of study might be too short to detect immunoreactive insulin (IRI) changes in the LR group because of the slow response of IRI to surgical stimulation. Cortisol and catecholamines released by noxious stimuli change conformation of the insulin receptor, resulting in insulin-resistance in peripheral tissue, i.e., relative insufficient effect of insulin. Furthermore, many hormones increasing plasma glucose concentrations are known to be released during surgical stress, whereas only insulin decreases plasma glucose. These mechanisms may be associated with the reason that increased insulin in the D2LR and D5LR groups did not prevent the increase in glucose. Our observations in infants are in contrast to a previous study, in which insulin secretion was suppressed during surgery in adults who were given a constant glucose infusion.

Whether preoperative fasting causes hypoglycemia in pediatric anesthesia is a problem that remains to be solved. Our findings are based on the standard nil per os guidelines currently recommended, and we used inpatients. The use of different nil per os guidelines and outpatients undergoing ambulatory surgery of shorter duration may have led to different results.

In the current study demonstrated that neither hypoglycemic nor hyperglycemic nor lipolytic response (lipid mobilization) was observed during infusion of solutions containing 2% glucose at a rate of 6 ml·kg⁻¹·h⁻¹. In minor surgery of 1.5 h duration, glucose infusion at a rate of 0.12 g·kg⁻¹·h⁻¹ may be sufficient to maintain normoglycemia and prevent compensatory increase in lipid mobilization in other-

References


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wise healthy, nonpremature infants. However, these results cannot be extrapolated to neonates, who might have a greater need for glucose. Further investigations are required to settle this issue.

References


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