

Effects of Oral Clonidine Premedication on Plasma Glucose and Lipid Homeostasis Associated with Exogenous Glucose Infusion in Children

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Background: Oral clonidine may influence plasma glucose and lipid homeostasis by modulating endocrinologic responses to surgical stress. The effect of oral clonidine premedication on plasma glucose and lipid homeostasis associated with exogenous glucose infusion were investigated in children undergoing minor surgery.

Methods: Otherwise healthy children (n, 120; aged 3–13 yr) were assigned randomly to six groups according to the glucose concentration of the intravenous solution (0%, 2%, or 5%, at a rate of $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and the preoperative medications (4 $\mu\text{g}/\text{kg}$ clonidine or placebo given 100 min before anesthesia) they were to receive. The plasma concentrations of glucose, nonesterified fatty acid, ketone bodies, epinephrine, norepinephrine, and cortisol were determined.

Results: Infusion of 5% glucose caused hyperglycemia (mean glucose concentration $>200 \text{ mg}/\text{dl}$) in six children receiving placebo and two receiving clonidine. Although the mean plasma glucose concentration increased in three placebo groups, it was unchanged and the plasma concentrations of total ketone bodies and nonesterified fatty acid were increased in children receiving clonidine and glucose-free solution. The plasma epinephrine, norepinephrine, and cortisol levels in children receiving placebo increased in response to surgery. Clonidine attenuated the increase in catecholamines and cortisol.

Conclusions: Oral clonidine premedication attenuated the hyperglycemic response, probably by inhibiting the surgical stress-induced release of catecholamines and cortisol. Infusion of 2% of glucose maintained plasma glucose concentrations within physiologic ranges in children receiving clonidine.

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dine. (Key words: α_2 -agonists; catecholamines; free fatty acids; growth hormone; insulin.)

ANESTHESIOLOGISTS have focused considerable interest on the propriety of intravenous glucose administration in pediatric surgery. We have shown that an intraoperative infusion of 2% or less of glucose solution at a rate of $6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ is appropriate for glucose and lipid homeostasis for long periods of surgery in children ages 1.5 to 9 yr and that an infusion of 5% glucose at this rate causes hyperglycemia.¹ It is well known that surgical stress stimulates the release of catecholamines and cortisol, both of which have anti-insulin action resulting in an increase of plasma glucose concentration.^{2,3} This hormonal response to surgical stress may explain previous findings that use of glucose-free solutions did not cause hypoglycemia during surgery.

Oral clonidine is a useful premedicant for children, providing excellent preoperative sedation,⁴ a reduced anesthetic requirement,⁵ and postoperative pain relief.⁶ The drug has two opposing effects on blood glucose. On the one hand it suppresses the stress responses to surgery by decreasing sympathoadrenal outflow.⁷ Premedication with clonidine inhibits the release of catecholamines and cortisol during surgery in adults⁸ and attenuates catecholamines response to tracheal intubation in children.⁹ This property of clonidine may attenuate the increase in plasma glucose in response to surgery. But clonidine also inhibits the release of insulin and potentiates the secretion of growth hormone.⁷ The modification of these two hormones by clonidine may contribute to the increase in plasma glucose concentrations. Thus oral clonidine may affect plasma glucose homeostasis in children. To test this hypothesis, we investigated the effect of oral clonidine on plasma glucose homeostasis associated with exogenous glucose administration in children undergoing minor surgery. This comparative analysis enabled us to determine the

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concentration of glucose solution that is appropriate to maintain plasma glucose concentration in this setting.

Materials and Methods

After we received institutional approval and informed consent from the parents of all children, we enrolled 120 otherwise healthy children (inpatients classified as American Society of Anesthesiologists physical status I) who ranged in age from 3 to 13 yr in our study. All of the children underwent elective ophthalmologic, urogenital, general (herniorrhaphy or hernioplasty), or otorhinolaryngologic surgery with minimal blood loss. All children were prohibited from eating solid food or drinking milk products after midnight but were instructed to ingest a moderate volume (5–6 ml/kg) of 5% glucose dissolved in water 3 h before the induction of anesthesia. A venous blood sample was taken at the ward before premedication. Children were premedicated orally with 4 µg/kg clonidine (n = 60; clonidine–0% dextrose, clonidine–2% dextrose, and clonidine–5% dextrose groups) or placebo (n = 60; placebo–0% dextrose, placebo–2% dextrose, and placebo–5% dextrose groups) approximately 100 min before induction of anesthesia. No other premedicants were administered. The induction of anesthesia in all cases began at 8:30 A.M. Anesthesia was induced with sevoflurane and nitrous oxide (N₂O) in oxygen. Catheters were inserted into the antecubital vein of both arms and into the radial artery after loss of consciousness. One venous catheter and arterial catheters were used for blood sampling, and infusion was started through the other venous line. The children were randomly divided into six groups of 20 patients each according to the combination of premedication and glucose concentrations infused as follows: Lactated Ringer's solution alone was infused in the placebo–0% dextrose and clonidine–0% dextrose groups. The placebo–2% dextrose and clonidine–2% dextrose groups received infusions of lactated Ringer's solution containing 2% glucose. In the placebo–5% dextrose and clonidine–5% dextrose groups, children received infusions of lactated Ringer's solution containing 5% glucose. All fluids were infused at a rate of 6 ml·kg⁻¹·h⁻¹ until 1 h after the completion of anesthesia. This infusion rate was recommended by Berry[#] for children undergoing minor surgery. The glu-

cose infusion rates in the 0%, 2%, and 5% glucose solutions were zero, 0.12, and 0.30 g·kg⁻¹·h⁻¹, respectively. Atropine (0.01 mg/kg) was given intravenously, and tracheal intubation was facilitated with 0.1 mg/kg vecuronium bromide. Anesthesia was maintained with 1–2.5% sevoflurane and 60% N₂O in oxygen to maintain hemodynamic stability by independent anesthetists who were blinded to the nature of the premedication. The endpoint of intraoperative hemodynamics was maintenance of blood pressure and heart rate within 25% of preinduction values. Muscle relaxation was supplemented with intermittent administration of vecuronium as needed. No patient received blood transfusions. Body temperature was monitored using a rectal probe and maintained at 37.1–37.8°C. After surgery, the trachea was extubated in the operating room after residual neuromuscular blockade had been antagonized with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Apart from the drugs just noted, no drugs, including vasoactive agents, were administered to any patient. In all children, the postoperative course was uncomplicated.

Measurements

The first venous blood sample was taken before premedication in the wards *via* venous puncture. The subsequent blood samples were obtained at the induction before the intravenous infusion, at the end of surgery, and 1 h after surgery through an indwelling catheter. All blood samples were centrifuged within 10 min of collection, and the plasma was separated and stored at –70°C until analysis. Plasma glucose concentrations were estimated using a hexokinase method.² Hypoglycemia was defined as a plasma glucose concentration <50 mg/dl,¹⁰ and hyperglycemia was defined as >200 mg/dl.¹¹ The plasma concentrations of nonesterified fatty acid and total ketone bodies were measured according to the methods of Itaya and Ui¹² and Harano *et al.*,¹³ respectively. Plasma insulin, cortisol, and growth hormone concentrations were quantified using radioimmunoassay kits supplied by Dainabot (Insulin-Riabeed; Dainabot, Tokyo, Japan), Baxter (Gamma-Coat Cortisol; Baxter, Deerfield, IL), and Daiichi Radioisotope (GH kit Daiichi; Daiichi Radioisotope, Tokyo, Japan), respectively. Plasma catecholamine concentrations were determined using reverse-phase high-performance liquid chromatography with electrochemical detection and an internal standard using the method described by Krstulovic¹⁴ and Causon and Carruthers.¹⁵

Arterial blood gases obtained from the arterial catheter were analyzed (pH, carbon dioxide and oxygen ten-

[#] Berry FA: Fluid and electrolyte therapy in pediatrics. 1995 ASA Annual Refresher Course Lectures, Lecture 232. Atlanta, 1995, pp 1–7

sions, and base excess [BE]) using an ABL3 analyzer (Radiometer, Copenhagen, Denmark) at induction of anesthesia, at the end of surgery, and 1 h after surgery.

Statistics

Statistical analysis for parametric data was performed using repeated measures analysis of variance with Bonferroni correction for between-group comparisons throughout the study periods, and thereafter repeated measures analysis of variance for within-group comparisons and a one-way analysis of variance for between-group comparisons at each treatment interval. Nonparametric (distribution) data were analyzed using Fisher's exact test. Differences were considered significant at $P < 0.05$.

Results

The age, weight, anesthesia and operation time, and volume of clear fluids ingested were 8.4 ± 2.9 yr, 31.3 ± 4.2 kg, 138 ± 42 min, 102 ± 34 min, and 5.8 ± 1.2 ml/kg (means \pm SD), respectively, and did not differ significantly among the groups. The total dose of glucose administered (mean \pm SD) was 385 ± 93 , 985 ± 198 , 395 ± 85 , and 960 ± 162 mg in the placebo-2% dextrose, placebo-5% dextrose, clonidine-2% dextrose, and clonidine-5% dextrose groups.

Plasma Glucose Homeostasis

No children became hypoglycemic at any time during the study. There was no significant difference in plasma glucose concentrations before premedication or at induction of anesthesia among the six groups (fig. 1A). In the placebo-5% dextrose group, the plasma glucose concentrations markedly increased during glucose infusion, reaching the hyperglycemic level. In the clonidine-0% dextrose group, the mean plasma glucose concentrations remained unchanged during the study and decreased slightly after surgery. Compared with the placebo-2% dextrose and placebo-5% dextrose groups, the magnitude of the increases in plasma glucose concentrations in the clonidine-2% dextrose and clonidine-5% dextrose groups was smaller during and after surgery.

In the clonidine-0% dextrose group, 7 of 20 children had an intraoperative decrease in plasma glucose concentration (fig. 2). Plasma glucose concentrations in all of the patients in the other five groups increased during surgery. Six and two patients in the placebo-5% dex-

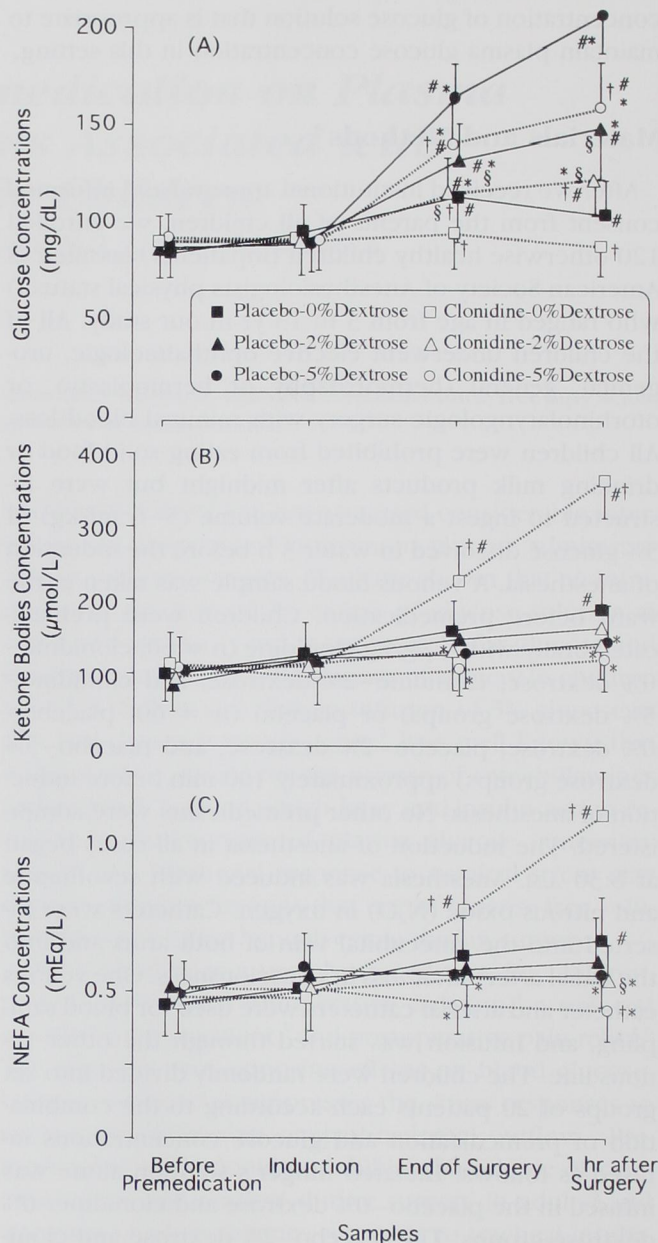


Fig. 1. Time course of plasma glucose (A), total ketone bodies (B), and nonesterified fatty acids (NEFA) concentrations (C) for six groups of children. Data are means \pm SD ($n = 20$ for each group). Some bars are omitted for clarity. $\#P < 0.05$ compared with basal values within groups; $*P < 0.05$ compared with the placebo-0% dextrose group (for other placebo groups) or the clonidine-0% dextrose group (for other clonidine groups); $\dagger P < 0.05$ for the clonidine compared with the placebo groups with the same infusion; $\S P < 0.05$ for the 2% dextrose group compared with the 5% dextrose group. The normal range of plasma total ketone body concentrations is $50\text{--}200 \mu\text{M}$. The normal range of plasma NEFA values is $0.25\text{--}0.9 \text{ mEq/L}$.

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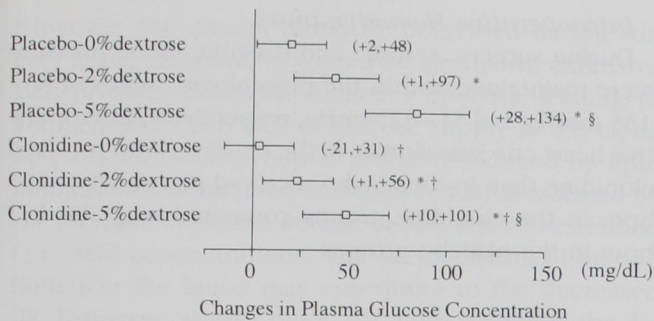


Fig. 2. Intraoperative changes in plasma glucose concentration. Data are expressed as means \pm SD with ranges shown in parenthesis (minimum, maximum). * $P < 0.05$ compared with placebo-0% dextrose for the placebo groups or clonidine-0% dextrose for the clonidine groups; † $P < 0.05$ for the clonidine compared with the placebo groups with the same infusion; § $P < 0.05$ for the 2% dextrose group compared with the 5% dextrose group.

trose and clonidine-5% dextrose groups, respectively, had hyperglycemia at the end of surgery. Hyperglycemia occurred 1 h after surgery in 11 and 3 children in the placebo-5% dextrose and clonidine-5% dextrose groups, respectively. Children who received the 2% glucose solution did not become hyperglycemic with either preoperative medication.

Assessment of Lipid Mobilization

In the placebo-0% dextrose group, plasma concentrations of total ketone bodies and nonesterified fatty acid were slightly increased after surgery but remained within normal ranges. In contrast, these variables in the clonidine-0% dextrose group increased. No other groups had lipid mobilization (figs. 1B, 1C).

Plasma Hormone Concentrations

The plasma catecholamine levels in the three placebo groups increased in response to surgery and remained high after operation. Clonidine premedication decreased the plasma catecholamine concentrations at induction of anesthesia and suppressed the increase in catecholamine levels (fig. 3).

The plasma cortisol levels were similar among surgeries in all groups. In the three placebo groups, cortisol concentrations increased during surgery and decreased slightly after surgery (fig. 4A). The increase in cortisol levels during and after surgery were slightly attenuated by clonidine premedication.

The plasma insulin concentrations decreased slightly in the children receiving glucose-free solution regard-

less of the nature of their premedication (fig. 4B). Glucose infusion increased the plasma insulin concentrations during surgery. The changes do not seem to be physiologically significant. Oral clonidine premedication did not change insulin concentrations in response to glucose infusion.

Plasma growth hormone concentrations increased after oral clonidine premedication (fig. 4C). Plasma growth hormone concentrations remained high during and after surgery. However, the changes were slight and there were no significant differences in growth hormone levels during or after surgery among the six groups.

Arterial Blood Acid-Base Balance

The results of arterial blood gas analysis (pH, partial pressures of oxygen and carbon dioxide) were consis-

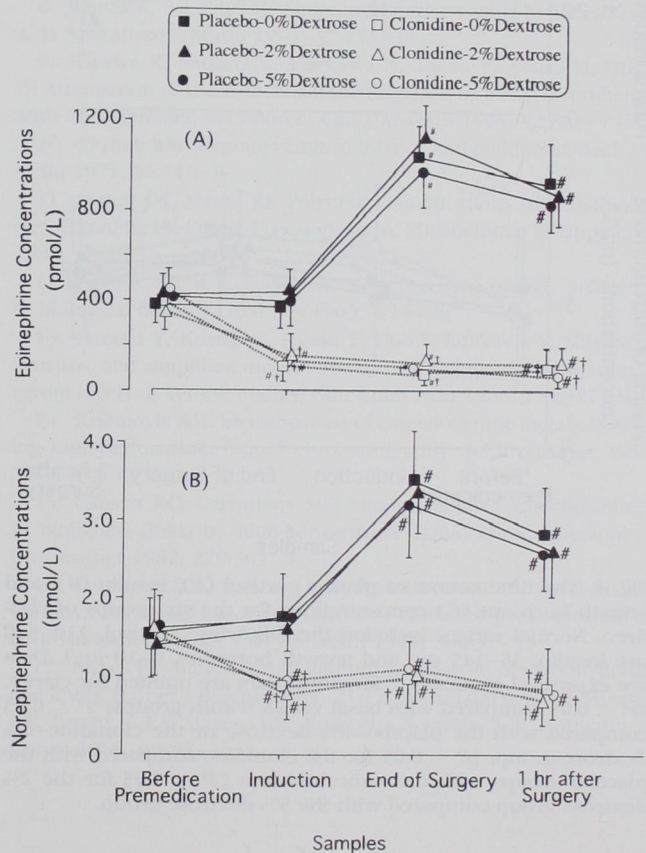


Fig. 3. The time course of plasma epinephrine (A) and norepinephrine (B) concentrations for the six groups of children. Data are means \pm SD. Some bars are omitted for clarity. The normal range of plasma epinephrine is 170–520 pm. The normal range of norepinephrine is 1.3–2.8 nm. # $P < 0.05$ compared with basal values within groups; † $P < 0.05$ for the clonidine compared with the placebo groups with the same infusion.

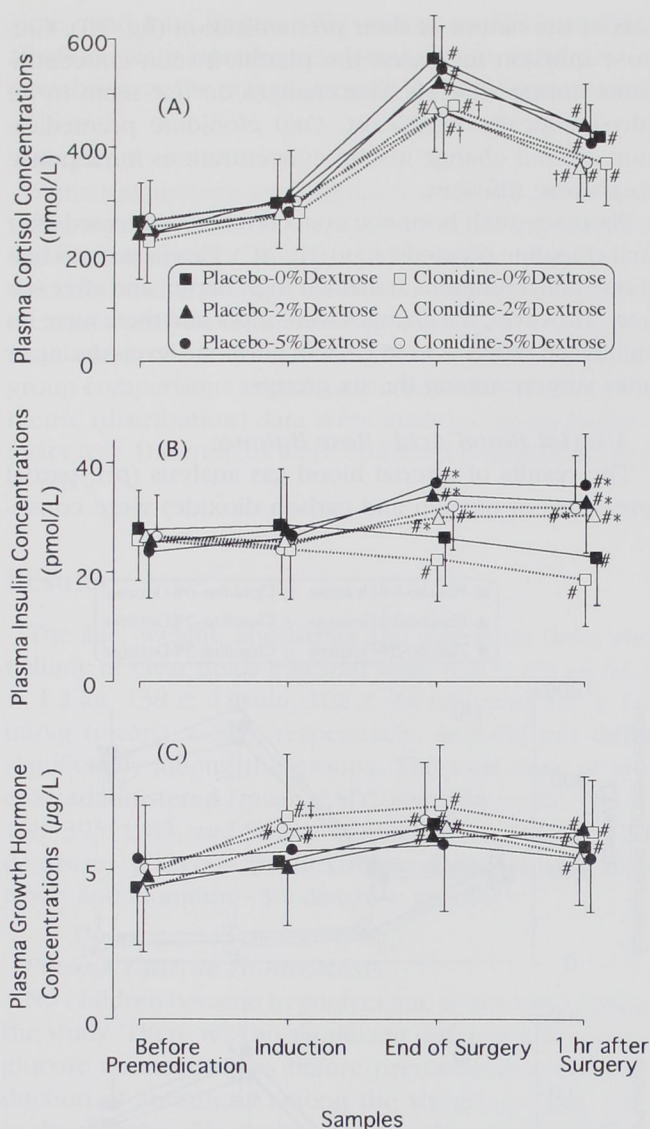


Fig. 4. The time course of plasma cortisol (A), insulin (B), and growth hormone (C) concentrations for the six groups of children. Normal ranges included the following: cortisol, 110–520 nm; insulin, 35–145 pm; and growth hormone, 0–10 µg/L. Data are expressed as means \pm SD. Some bars are omitted for clarity. # $P < 0.05$ compared with basal values within groups; * $P < 0.05$ compared with the placebo–0% dextrose or the clonidine–0% dextrose group; † $P < 0.05$ for the clonidine compared with the placebo groups with the same infusion; § $P < 0.05$ for the 2% dextrose group compared with the 5% dextrose group.

tently within normal ranges throughout the study. The BE was significantly decreased in the clonidine–0% dextrose group at the end of surgery compared with the values at induction of anesthesia (-1.3 ± 0.2 to -2.4 ± 0.4), whereas it did not change significantly in the other groups (with a range of -1.1 to -2).

Intraoperative Hemodynamics

During surgery, systolic and diastolic blood pressure were maintained within the physiologic ranges of 83–135 mmHg and 51–82 mmHg, respectively. Intraoperative heart rate was slower in the children who received clonidine than in those who received placebo: 60–103 bpm in the clonidine groups compared with 75–121 bpm in the placebo groups.

Discussion

In the present study, we found that oral clonidine premedication attenuated the hyperglycemic response to surgery and glucose infusion. This suppressive effect of clonidine on hyperglycemia may be due to an inhibition of the surgical stress-induced release of catecholamine and cortisol. In adults undergoing neurosurgery, oral clonidine (approximately 4.6 µg/kg) decreased plasma glucose levels during the recovery period compared with placebo, probably by suppressing plasma cortisol levels.¹⁶ Our observation in children confirmed this finding in adults.

Clonidine has been reported to inhibit the release of insulin.⁷ In the current study, it failed to suppress the increase in plasma insulin concentrations in response to glucose infusion. This may contribute in part to the attenuation of the hyperglycemic response to glucose infusion by clonidine. In contrast, the hyperglycemia-blunting effect of clonidine may be disadvantageous when no glucose is infused perioperatively. As in many recent studies, all of the children in the placebo–0% dextrose group responded to surgery with an increase in plasma glucose concentrations. However, oral clonidine premedication suppressed the increase in plasma glucose during surgery in children who did not receive glucose infusion. These findings suggest that children who are premedicated with clonidine and receive intraoperative glucose-free solution have a potential risk for hypoglycemia during long operations. Plasma growth hormone concentrations slightly increased after oral clonidine premedication. Although growth hormone increases plasma glucose concentrations, it seems to play only a minor role in regulating plasma glucose levels in this stressful setting.

We found that children in the placebo–0% dextrose group did not become hypoglycemic perioperatively. We also observed lipid mobilization without clinical implication (physiologic ranges of plasma ketone bodies and nonesterified fatty acid levels) in this population.

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However, the arterial blood BE decreased during surgery in the clonidine-0% dextrose group. An extensive lack of glucose supply enhances lipolysis, leading to ketogenesis.¹⁷ This lack of glucose supply in the clonidine-0% dextrose group is probably induced by lipid mobilization to maintain normoglycemia, as assessed by the increase in plasma ketone bodies and nonesterified fatty acid concentrations. The accumulation of ketone bodies in the blood may contribute to the decreased BE. However, arterial blood pH did not parallel the decrease in BE. This decreased BE does not seem to be great enough to have any clinical implication. Administration of fluids containing glucose to children who received oral clonidine prevented development of acidosis, probably due to inhibition of ketogenesis.

In conclusion, we found that oral clonidine (4 µg/kg) premedication attenuated the hyperglycemic response to surgical stress and to infusion of glucose in children undergoing minor surgery, probably by inhibiting the surgical stress-induced release of catecholamine and cortisol. However, oral clonidine premedication did not completely prevent hyperglycemia associated with infusion of 5% glucose. Furthermore, in the children who received oral clonidine and infusion of a glucose-free solution, plasma glucose concentrations did not increase and lipid mobilization occurred. In otherwise healthy children who received oral clonidine before operation and underwent minor surgery of short duration (approximately 1.7 h), infusion of 2% glucose at a rate of 6 ml · kg⁻¹ · h⁻¹ maintained plasma glucose concentration within physiologic ranges and did not cause a compensatory increase in lipid mobilization. However, we cannot extrapolate our results to children who undergo major surgery of long duration with more severe stress; further investigations are required to explore that issue.

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