Dexamethasone reduces gut permeability in pediatric cardiac surgery

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Objectives: Little attention has been paid to the effect of the systemic inflammatory response syndrome on intestinal dysfunction in the postoperative period. Several proinflammatory cytokines have been reported to increase the permeability of intestinal mucosa in vitro. We investigated the effect of dexamethasone on gut permeability in pediatric patients undergoing cardiac surgery by using the dual sugar permeability test and absorption of 2 other saccharides.

Methods: Thirty-four patients scheduled for cardiac surgery with cardiopulmonary bypass were prospectively randomized to either act as control subjects or to receive dexamethasone (1 mg · kg$^{-1}$) during induction of anesthesia. Intestinal permeability was measured with 3-O-methyl-D-glucose, D-xylose, L-rhamnose, and lactulose administered orally after induction of anesthesia and 12 and 24 hours later.

Results: Lactulose/rhamnose ratios were increased from the outset in both groups (mean 0.57 [95% confidence interval, 0.24-0.91] for the control group and 0.76 [95% confidence interval, 0.35-1.17] for patients receiving dexamethasone). Although the ratios decreased 12 hours (0.29 [95% confidence interval, 0.17-0.42]) and 24 hours later (0.17 [95% confidence interval, 0.08-0.15]) in the dexamethasone group, in the control group there was a rise at 12 hours (0.77 [95% confidence interval, 0.17-1.64]), with a slight reduction 24 hours later (0.46 [95% confidence interval, 0.06-0.85]).

Conclusions: Infants and children undergoing cardiac surgery with cardiopulmonary bypass show a significant reduction in gut permeability when dexamethasone is used during induction of anesthesia. Dexamethasone does not affect the intestinal barrier at the functional level, as assessed on the basis of 3-O-methyl-D-glucose and D-xylose absorption.

Cardiopulmonary bypass (CPB) can trigger a systemic inflammatory response syndrome. This might result postoperatively in fever, fluid retention, and pulmonary, renal, cardiac, and cerebral dysfunction. Little attention has been paid to the effect of CPB and the associated systemic inflammatory response on intestinal dysfunction in the postoperative period.

The postoperative release of inflammatory mediators after pediatric cardiac surgery has been reviewed extensively elsewhere. Several proinflammatory cytokines have been reported to increase the permeability of intestinal mucosa in vitro. Anti-inflammatory cytokines, on the other hand, ameliorated induced gut epithelial hyperpermeability in vitro. The mechanisms involved in this phenomenon are not totally clear.

Intestinal permeability can be evaluated noninvasively by measuring the urinary excretion of orally administered, water-soluble, nondegradable test molecules. This barrier function test is based on the comparison of intestinal permeation of larger molecules with that of smaller molecules by measuring the ratio of their permeability.
urinary excretion. These 2 types of molecules follow different routes of intestinal permeation: the larger molecules are assumed to permeate paracellularly, and the smaller molecules are assumed to permeate transepithelially. Preabsorption factors, such as gastric emptying, dilution by means of secretion, and intestinal transit time, and postabsorption factors, such as systemic distribution and renal clearance, are assumed to affect both molecules equally. Four saccharides, 3-O-methyl-D-glucose (molecular weight, 194 d), D-xylene (molecular weight, 150 d), L-rhamnose (molecular weight, 342 d) are used to assess active carrier-mediated, passive carrier-mediated, transcellular, and paracellular transport, respectively, in the small intestine. Intestinal permeability is considered to be normal if the lactulose (percentage recovery)/rhamnose (percentage recovery; L/R) ratio is less than 0.05.\textsuperscript{5} Intestinal absorptive capacity for saccharides is considered to be normal when the minimum recoveries of D-glucone, D-xylose, and L-rhamnose are on average up to 8 times higher than in healthy neonates.\textsuperscript{8}

The possible clinical applications of the dual sugar permeability test (DSPT) have not been explored in this group of patients. Gastrointestinal complications in the postoperative period are rare but are accompanied by devastating consequences, such as necrotizing enterocolitis in patients with the hypoplastic left heart syndrome.\textsuperscript{9} The DSPT might be used as a surrogate marker to test the effect of drugs or novel therapies on the splanchnic circulation.

The use of steroids in cardiac surgery remains controversial.\textsuperscript{10} There is evidence in the literature that steroids, administered before the start of CPB, reduce the release of proinflammatory mediators associated with both adult and pediatric cardiac surgery.\textsuperscript{11,12} However, the benefits of steroids on clinical outcomes are not fully proved.\textsuperscript{13}

The aim of our study was to observe the effect of a single dose of dexamethasone before CPB starts on the changes in gut permeability in pediatric cardiac surgery with the DSPT.

**Patients and Methods**

After obtaining approval from the local ethics committee and informed consent from the parents or legal guardians, we enrolled 34 patients in this prospective, randomized, single-blind interventional study. Patients were allocated to receive either dexamethasone (1 mg · kg\textsuperscript{-1} · d) during induction of anesthesia) or act as control subjects. The use of placebo is not allowed by our local ethics committee. Patients received a premedication consisting of oral atropine (0.02 mg · kg\textsuperscript{-1}) and midazolam (0.5 mg · kg\textsuperscript{-1}) 30 minutes before induction of anesthesia. Anesthesia was induced with sevoflurane, followed by a bolus of sufentanil (1 μg · kg\textsuperscript{-1}) and pancuronium (0.2 mg · kg\textsuperscript{-1}). Maintenance of anesthesia consisted of a combined continuous infusion of midazolam (0.2 mg · kg\textsuperscript{-1} · h) and sufentanil (2 μg · kg\textsuperscript{-1} · h). The lungs of the patients were mechanically ventilated with a mixture of oxygen and air. Mechanical ventilation was maintained until CPB concluded. After heparin administration (3 mg · kg\textsuperscript{-1}) and aorta cannulation, CPB was instituted with a Dideco hollow-fiber oxygenator (Dideco SpA, Mirandola, Italy) with a blood flow of between 200 and 300 mL · kg\textsuperscript{-1} · min\textsuperscript{-1}. The prime volume, between 325 and 750 mL, according to the patient’s weight, contained lactate-free Ringer solution, albumin, mannitol, blood, and heparin. No steroids were added to the prime. Patients underwent modified ultrafiltration at the end of the surgical procedure. The effect of heparin was reversed with protamine sulfate in a ratio of 1 mg of protamine for 1 mg of heparin.

After induction of anesthesia 2 mL · kg\textsuperscript{-1} · h of the sugar solution was administered through a nasogastric tube. Urine was subsequently collected in a test tube in a urinary catheter for 3 hours, the total volume was recorded, and samples were stored at −20°C until analysis. This process was repeated 12 and 24 hours after induction of anesthesia. The sugar solution, prepared by the hospital pharmacy, contained 3-O-methyl-D-glucose (2 g · L\textsuperscript{-1}), D-xylose (5 g · L\textsuperscript{-1}), L-rhamnose (10 g · L\textsuperscript{-1}), and lactulose (50 g · L\textsuperscript{-1}). The osmolarity of the solution is approximately 240 mOsm · L\textsuperscript{-1}.

Sugar concentrations in urine were determined by gas chromatography, according to a slight modification\textsuperscript{14} of the procedure described by Jansen and colleagues.\textsuperscript{15} In brief, to an aliquot of urine corresponding to 0.5 μmol of creatinine, 30 μg of ribitol and 10 μg of trehalose (Sigma-Aldrich, St Louis, Mo) were added as internal standards (ribitol for the determination of 3-O-methyl-D-glucose, D-xylose, and L-rhamnose and trehalose for lactulose). The sample was dried, derivatized with 300 μL of Tri-Si TBT (Pierce, Rockford, Ill) at 100°C, and partly hydrolyzed with water. Subsequently, the intact sugar trimethylsilyl derivatives were extracted with hexane, and after concentrating, gas chromatographic analysis was performed on a 30-m capillary fused silica HP-1 column (Agilent, Palo Alto, Calif) by split injection. Quantification was performed after the construction of standard addition calibration curves.

The type of vasoactive drugs and their amounts were recorded after admission to the intensive care unit and 24 hours later. To quantify inotropic support, we calculated inotrope scores as the sum of all inotrope doses correcting for potency (dopamine and dobutamine = 1, milrinone = 15, epinephrine = 100).\textsuperscript{16} Fluid intake (including crystalloids, colloids, and blood products), output (urine, blood, and serous fluid loss), and balance were recorded over a 36-hour period after admission to the intensive care unit. Urea and creatinine concentrations were measured preoperatively, immediately after admission to the intensive care unit, and 24 hours later.

Data were analyzed with the statistical package SPSS v10 (SPSS, Inc, Chicago, Ill). Data are presented as means with 95% confidence intervals (CIs). Patient characteristics (age, weight, surgical times, and ventilator hours), fluid balance, and inotropic scores were analyzed with unpaired t tests. Because L/R ratios and percentage recovery of the other 2 sugars were not normally distributed, the data were first subjected to a natural logarithmic.
Results

Table 1 shows patient characteristics. Ventilator hours were similar in both groups. Inotropic scores are not significantly different either between the 2 groups at the same periods or within each group. The total fluid balance over the 36-hour study period was not significantly different between the 2 groups. The types of operations performed in each group are shown in Table 2. Table 3 shows the L/R ratios and percentage recovery of the 4 sugars throughout the study period. This is a prospective analysis showed that we needed a sample size of 34 to detect a difference in the L/R ratio of 0.02 with an α value of 0.05 and a power of 80%.

Discussion

We have shown in this study that dexamethasone administered before the commencement of CPB reduces postoperative gut permeability, as assessed by the DSPT.

There was an age and weight difference between the 2 groups. This could be seen as a limiting factor in the interpretation of the results. Univariate analysis showed that neither variable influenced either L/R ratios or percentage recovery of the other 2 sugars. The DSPT has been used to assess intestinal function in healthy neonates, in whom the L/R ratios were around 0.05.5 Similar values were found in children (range, 0.023-0.074; mean [SD], 0.047\( \pm \)0.018).6 Gut permeability has been investigated in adult patients undergoing coronary artery bypass surgery.17 L/R ratios increased immediately after surgical intervention, returning to normal values approximately 48 hours after the surgical procedure. The DSPT has also been used to test the beneficial effects of dopexamine over dopamine in the splanchinic circulation during adult coronary bypass surgery.18 The accuracy of the DSPT relies on the complete collection of urine samples during the study period. This is a
limiting factor on the applicability of the test in noncooperative patients without a urinary catheter. A high percentage of patients are discharged to the ward the day after surgical intervention, with consequent removal of urinary catheters. For this reason, we performed the test during the first 24 hours after the operation.

There has been criticism concerning the interpretation and significance of the DSPT in the literature. In an animal model it was shown that fluid loading increased the L/R ratios independent of changes in intestinal permeability. In an 8-hour period rats received a fluid bolus equivalent to twice the daily fluid oral intake. Put into perspective, this means an infant of 10 kg would receive approximately 2 L of fluid intravenously in an 8-hour period. We carefully documented the fluid balance during the study period. On average, patients received less than the daily maintenance fluid expected for their age.

The DSPT relies on the assumption that when lactulose and rhamnose are combined in the test solution at a fixed concentration ratio, the effect of preabsorption factors (gastric emptying, dilution by secretions, and intestinal transit...
time) and postabsorption factors (systemic distribution and renal clearance) will apply equally to both. Therefore, the L/R ratio is only influenced by the difference in gut permeability for each molecule.21

Percentage recovery of single markers might be influenced not only by the permeability of the intestinal mucosa but also by preabsorption and postabsorption factors. D-xylose and 3-O-methyl-D-glucose provide information about the functional state of the intestinal mucosa, whereas the L/R ratio is a reflection of the mucosal integrity at the morphologic level.

Percentage recoveries for D-xylose and 3-O-methyl-D-glucose did not differ substantially between the 2 groups. There is a trend toward normality through the study period, although at T24, percentage recoveries for both sugars are far from values expected in healthy children.

Our study has shown that the use of dexamethasone improved gut permeability at the morphologic level in our patients. However, we have no explanation as to why dexamethasone did not affect the intestinal barrier at the functional level. An L/R ratio of 0.46 is nearly 10 times the normal value and is a reflection of a highly permeable intestinal mucosa. Whether this implies that the patient is at higher risk for intestinal bacterial translocation and subsequent sepsis or intestinal ischemia is not clear. The converse is surely true. Patients given a diagnosis of necrotizing enterocolitis have consistently high L/R ratios.22

A likely explanation for our results is the effect that dexamethasone exerts in the postoperative production of proinflammatory cytokines. The concentration of proinflammatory cytokines decreases when steroids are used before or at commencement of CPB. This has been demonstrated consistently in a number of studies.11,23 Several cytokines, including interleukin 1 (IL-1), IL-4, IL-6, IL-10, interferon γ, and tumor necrosis factor, have been reported to increase intestinal permeability in vitro.3 IL-6, in particular, might be a mediator of intestinal mucosal injury in various conditions associated with transient mesenteric hypoperfusion and subsequent inflammation.24

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**Figure 3.** Changes of rhamnose percentage recovery in both groups. Values are expressed as means (95% CI). ●, T0; ■, T12; ▲, T24. *Statistical significance between groups.

**Figure 4.** Changes of D-xylose percentage recovery in both groups. Values are expressed as means (95% CI). ●, T0; ■, T12; ▲, T24. *Statistical significance between groups.

**Figure 5.** Changes of 3-O-methyl-D-glucose percentage recovery. Values are expressed as means (95% CI). µ, T0; ■ T12; ▲, T24. *Statistical significance between groups. 3OMG, 3-O-methyl-D-glucose.
A combined administration of steroids hours before the operation plus its addition to the pump prime appears to be more beneficial. Administration of steroids intravenously to patients hours before the surgical procedure is, however, often difficult for technical and logistical reasons. It has been standard practice in our institution to use dexamethasone during induction of anesthesia only in patients undergoing a period of circulatory arrest. The results of the present study are an encouragement to investigate whether adding steroids to the pump prime might provide a better improvement, faster improvement, or both in gut permeability.

Nevertheless, the use of dexamethasone in pediatric cardiac surgery remains a controversial issue. Lindberg and colleagues stated that omitting the use of dexamethasone in children weighing less than 10 kg scheduled for cardiac surgery is unethical. Schroeder and associates accepted that the lack of a control group without methylprednisolone is a limiting factor in their study. It is, according to them, standard practice to use steroids in these patients. However, there are no prospective or retrospective cohort studies that clearly show the influence of steroids on the clinical postoperative course. In the present study, none of the patients in the control group had gastrointestinal complications in the postoperative period, and the clinical parameters measured were not affected by dexamethasone.

Use of dexamethasone to improve intestinal absorption is not a new concept. As early as 1984, Bauer and coworkers noticed a reduction in the incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. Animal studies have shown repeatedly that in the immature animal dexamethasone reduces bacterial translocation in the gut and increases the length of the small intestine. The use of dexamethasone (0.5 to 1 mg·kg⁻¹·day⁻¹ for several days) to treat or prevent chronic lung disease in preterm infants is discouraged after intensive review of the literature. Our patients were not premature; they were exposed to enteral feeding, and their intestinal walls were far from immature.

The mechanisms by which dexamethasone exerts its effects on the intestinal mucosa are not totally elucidated. Further research is thus necessary.

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References

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