Gut permeability and myocardial damage in paediatric cardiac surgery

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CHAPTER 3

Dexamethasone reduces gut permeability in paediatric 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 paediatric patients undergoing cardiac surgery using the dual sugar permeability test and absorption of two other saccharides.

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

Results: Lactulose/rhamnose ratios were elevated from the outset in both groups; (mean (95% Confidence intervals)) 0.57 (0.24 – 0.91) for the control group and 0.76 (0.35 – 1.17) for patients receiving dexamethasone. While the ratios decreased 12 h (0.29 (0.17 – 0.42)) and 24 h later (0.17 (0.08 – 0.15)) in the dexamethasone group, in the control group there was a rise at 12 h (0.77 (0 – 1.64)), with a slight reduction 24 h later (0.46 (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 anaesthesia. Dexamethasone does not affect the intestinal barrier at the functional level as assessed by (3-O-methyl-D-glucose and D-xylose absorption).

Cardiopulmonary bypass (CPB) can trigger a systemic inflammatory response syndrome. This may result postoperatively in fever, fluid retention and pulmonary, renal, cardiac and cerebral dysfunction.[1] 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 paediatric cardiac surgery has been reviewed extensively elsewhere.[2] Several proinflammatory cytokines have been reported to increase the permeability of intestinal mucosa in vitro.[3] Antiinflammatory cytokines on the other hand ameliorated induced gut epithelial hyperpermeability in vitro.[4] 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, non-degradable test molecules.[5,6] 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 urinary excretion. These two types of molecules follow different routes of intestinal permeation: the larger molecules are assumed to permeate paracellularly, and the smaller molecules transcellularly. Preabsorption factors such as gastric emptying, dilution by secretion and intestinal transit time, and post-absorption 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 Da), D-xylose (molecular weight 150 Da), L-rhamnose (R, molecular weight 164 Da) and lactulose (L, molecular weight 342 Da) are employed 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 (% recovery)/rhamnose (% recovery) (L/R) ratio is below 0.05.[5] Intestinal absorptive capacity for saccharides is considered to be normal when the minimum recoveries of D-xylose (passive carrier-mediated transport) and 3-O-methyl-D-glucose (active carrier–mediated transport) are around 10% and 30% respectively.[7] A previous study has shown that preoperative L/R ratios in patients with congenital heart defects are on average up to eight times higher than in healthy neonates.[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 with devastating consequences, such as necrotizing enterocolitis in patients with the hypoplastic left heart syndrome.[9]

The DSPT may 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.[10] There is evidence in the literature that steroids, given before the start of CPB, reduce the release of proinflammatory mediators associated with both adult and paediatric cardiac surgery.[11,12] However the benefits of steroids on clinical outcome are not totally proven.[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 paediatric cardiac surgery using the DSPT.

Materials and methods

After approval from the local ethics committee and informed consent from the parents or legal guardians, 34 patients were enrolled in this prospective, randomized, single blinded interventional study. Patients were allocated to receive either dexamethasone (1 mg kg^{-1} during induction of anaesthesia) or act as controls. The use of placebo is not allowed by our local ethics committee. Patients received a premedication consisting on oral atropine (0.02 mg kg^{-1}) and midazolam (0.5 mg kg^{-1}) 30 min before induction of anaesthesia. Anaesthesia was induced with sevoflurane followed by a bolus of sufentanil (1 μg kg^{-1}) and pancuronium (0.2 mg kg^{-1}). Maintenance of anaesthesia consisted on a combined continuous infusion of midazolam (0.2 mg kg^{-1} h^{-1}) and sufentanil (2 μg kg^{-1} h^{-1}). The lungs of the patients were mechanically ventilated with a mixture of oxygen and air. Mechanical ventilation was maintained until CPB commenced. After heparin administration (3 mg kg^{-1}) and aorta cannulation, CPB was instituted with a Dideco hollow fibre oxygenator with a blood flow between 200 and 300 ml kg^{-1} min^{-1}.

The prime volume, between 325 and 750 ml according to the patient's weight, contained lactate-free Ringer's solution, albumin, mannitol, blood and heparin. No steroids were added to the prime. Patients underwent modified ultra-filtration at the end of the surgical procedure. The effect of heparin was reversed with protamine sulphate in a ratio of 1 mg protamine for 1 mg heparin. After induction of anaesthesia, 2 ml kg^{-1} of the sugar solution was administered through a nasogastric tube. Urine was subsequently completely collected through a urinary catheter for 3 h, the total volume was recorded and samples were stored at -20° C until analysis. This process was repeated 12 and 24 h after induction of anaesthesia.

The sugar solution, prepared by the hospital pharmacy, contained 3-O-methyl-D-glucose (2 g litre^{-1}), D-xylose (5 g litre^{-1}), L-rhamnose (10 g litre^{-1}) and lactulose (50 g litre^{-1}). The osmolarity of the solution is approximately 240 mOsm l^{-1}.

Sugar concentrations in urine were determined by gas chromatography following a slight modification[14] of the procedure described by Jansen and colleagues.[15] Briefly, to an aliquot of urine corresponding to 0.5 μmol of creatinine 30 μg of ribitol and 10μg of trehalose (Sigma-Aldrich, St. Louis, USA) 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, derivatised with 300μl Tri-Sil TBT (Pierce, Rockford, USA) at 100° C and partly hydrolyzed with water. Subsequently the intact sugar trimethylsilyl (TMS) 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, USA) using split injection. Quantification was performed after the construction of standard addition calibration curves. The type of vasoactive drugs and their amount were recorded after admission to the intensive care unit and 24 h later.

To quantify inotropic support, inotrope scores were calculated as the sum of all inotrope doses correcting for potency (dopamine, dobutamine =1, milrinone = 15, epinephrine = 100).[16] Fluid intake (including crystalloids, colloids and blood products), output (urine, blood and serous fluid loss) and balance were recorded over a 36 h period following admission to the intensive care unit. Urea and creatinine concentrations were measured preoperatively, immediately after admission to the intensive care unit and 24 h later.

Statistical analysis

Data were analyzed with the statistical package SPSS v10. Data are presented as mean (95% confidence intervals). Patients characteristics (age, weight, surgery times and ventilator hours), fluid balance and inotropic scores were analyzed by unpaired t test. Because L/R ratios and percentage recovery of the other two sugars were not normally distributed, the data were first subjected to a natural logarithmic transformation. We used repeated measures ANOVA to compare the two time points (T12 and T24) using dexamethasone as between subject factor.

Based on a previous study[6] that found a mean (SD) L/R ratio of 0.047 (0.018), 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 $\alpha = 0.05$ and a power of 80%.

Results

Table 1 shows patients characteristics. Ventilator hours are similar in both groups. Inotropic scores are not significantly different either between the two groups at the two time periods or within each group. The total fluid balance over the 36 hours study period was not significantly different between the two groups. The type of operations performed in each group is shown in table 2. Table 3 shows the L/R ratios and percentage recovery of the four sugars throughout the study period together with the P value for each parameter. Differences in L/R ratios between the two groups were statistically significant. Differences in percentage recovery for rhamnose and 3-O-Methyl-D-Glucose were also significant between the two groups. There were no significant differences in the percentage recovery of lactulose and D-xylose between the two groups.

	No dexamethasone	Dexamethasone	P values
Number of patients	17	17	
Age (months)	12 (5 - 19)	4 (2 - 6)	0.02
Sex (M/F)	6/11	7/10	0.46
Weight (kg)	7 (5 – 9)	5 (4 - 6)	0.01
Surgery time (min)	181 (152 – 211)	190 (145 – 234)	0.65
Bypass time (min)	118 (100 – 135)	118 (87 – 149)	0.66
Aortic clamp time (min)	64 (46 – 83)	78 (52 – 104)	0.58
Ventilator hours	52 (33 – 71)	81 (27 – 135)	0.79
Inoscore	4 (2 – 6)	7 (2 – 11)	0.83
Inoscore 24 hours	6 (3 – 10)	7 (1 – 13)	0.58
Balance (ml kg^{-1})	29 (3 – 55)	33 (12 – 54)	0.89

Table 1: Patient characteristics. Values expressed as mean (95% confidence intervals).

	No dexamethasone	Dexamethasone
VSD	7	6
ToF	1	1
TAPVC	2	2
Arterial switch	0	4
Rastelli	0	1
PA, MAPCA	0	1
AVSD	2	0
AVA	1	0
BCPA	2	1
MVA	2	1
Total	17	17

Table 2: Surgical procedures. Ventricular septal defect (VSD), Tetralogy of Fallot (ToF), Total anomalous pulmonary venous connection (TAPVC), Atrioventricular septal defect (AVSD), aortic valve anuloplasty (AVA), bidirectional cavopulmonary anastomosis (BCPA), mitral valve annuloplasty (MVA), major aortopulmonary collateral arteries (MAPCA), pulmonary atresia (PA).

Urea and creatinine concentrations remained within the normal clinical range throughout the study period. In the control group urea concentrations (normal range 0.7 to 6.7 mmol l^{-1}) were 4.8 (4 – 5.5) mmol l^{-1} preoperatively, 4.1 (3.4 – 4.8) mmol l^{-1} immediately after the operation and 5.9 (4.9 – 6.8) mmol l^{-1} 24 h later. In the dexamethasone group there were 4 (3.4 – 4.6) mmol l^{-1} preoperatively, 4 (3.3 – 4.7) mmol l^{-1} immediately after the operation and 5.5 (4.7 – 6.3) mmol l^{-1} 24 h later. Creatinine concentrations (normal value less than 70 μmol l^{-1}) were in the control group 41 (37 – 45) μmol l^{-1} preoperatively, 40 (37 – 44) μmol l^{-1} immediately after the operation and 52 (41 – 63) μmol l^{-1} 24 h later.

In the dexamethasone group there were 31 (25 – 38) μmol l^{-1} preoperatively, 31 (26 – 37) immediately after the operation and 34 (28 – 39) μmol l^{-1} 24 h later. None of the patients developed acute renal failure during the study period. Figures 1 to 5 are graphical representations of the changes in L/R ratios, and percentage recovery for lactulose, rhamnose, D-xylose and 3-O-methyl-D-glucose in both groups.

	T0	T12	T24	P value
L/R ratios				
No dexamethasone	0.57 (0.24 – 0.91)	0.77 (0 – 1.64)	0.46 (0.06 – 0.85)	
Dexamethasone	0.76 (0.35 – 1.17)	0.29 (0.17 – 0.42)	0.17 (0.08 – 0.15)	0.019
Lactulose				
No dexamethasone	0.07 (0.02 – 0.12)	0.31 (0.22 – 0.4)	0.87 (0.51 – 1.23)	
Dexamethasone	0.08 (0.02 – 0.14)	0.62 (0.34 – 0.89)	1.07 (0.11 – 2.04)	0.056
Rhamnose				
No dexamethasone	0.16 (0.02 – 0.30)	1.44 (0.68 – 2.2)	4.59 (2.23 – 6.94)	
Dexamthasone	0.16 (0.02 – 0.31)	3.02 (1.36 – 4.69)	6.18 (3.35 – 9)	0.047
D-xylose				
No dexamethasone	0.29 (0.14 – 0.45)	1.58 (0.42 – 2.75)	5.69 (2.41 – 8.96)	
Dexamethasone	0.34 (0.08 – 0.60)	2.96 (1.83 – 4.09)	5.47 (2.59 – 8.34)	0.056
3OMG				
No dexamethasone	0.38 (0.12 – 0.64)	3.37 (1.21 – 5.54)	14.42 (6.19 – 22.6)	
Dexamethasone	0.33 (0.09 – 0.57)	7.32 (3.32 – 11.33)	13 (6.59 – 19.42)	0.041

Table 3: Lactulose/rhamnose ratios (L/R) and percentage recovery for lactulose, rhamnose, D-xylose and 3-O-methyl-glucose (3OMG) without and with dexamethasone. Values are expressed as mean (95% confidence intervals). * Denotes statistical significance between groups

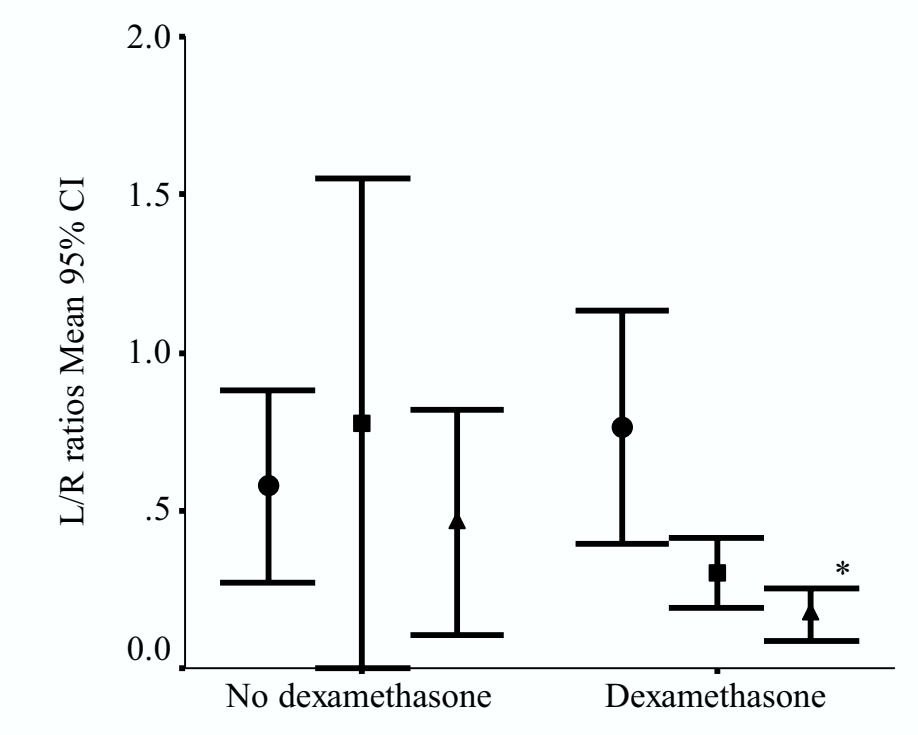

Fig 1: Changes in L/R ratios in both groups. Values expressed as mean 95% CI. (●) T0, (■) T12, (▲) T24.* Denotes statistical significance between groups.

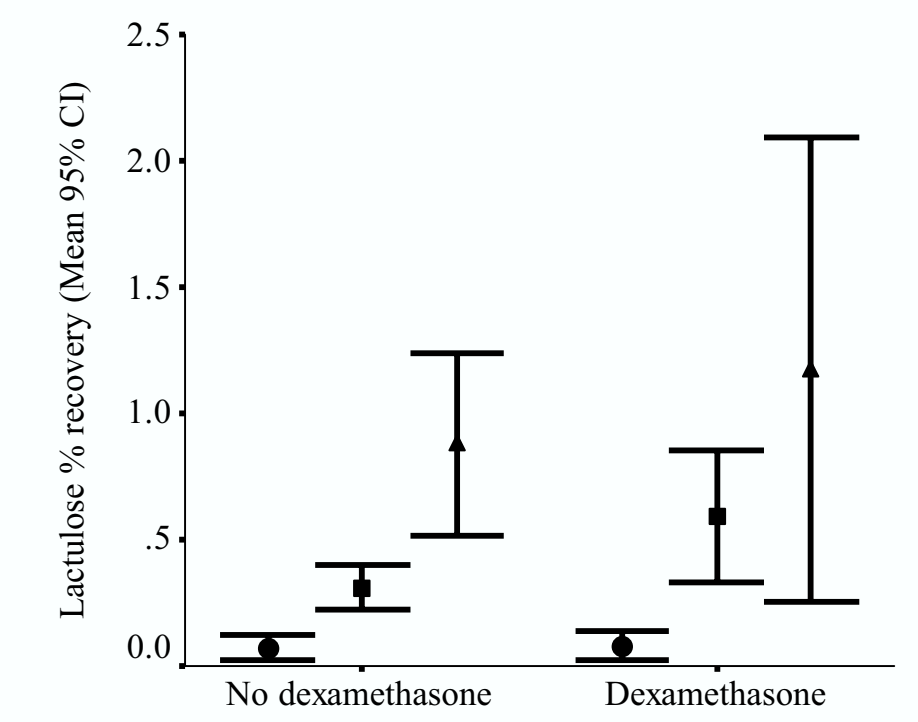

Fig 2: Changes of lactulose percentage recovery in both groups. Values expressed as mean 95% CI. (●) T0, (■) T12, (▲) T24.* Denotes statistical significance between groups.

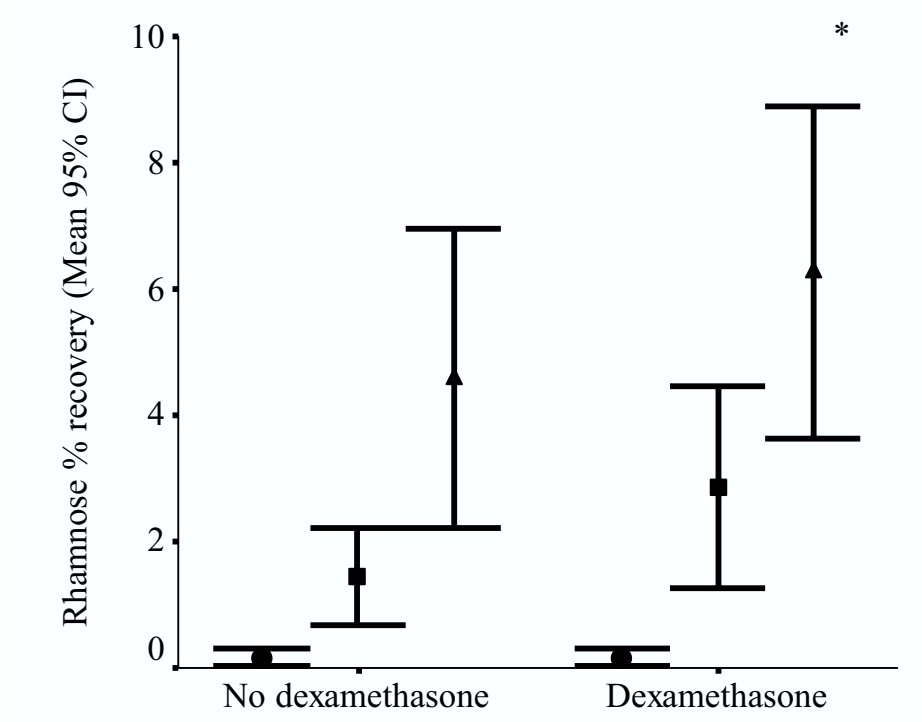

Fig 3: Changes of rhamnose percentage recovery in both groups. Values expressed as mean 95% CI. (●) T0, (■) T12, (▲) T24.* Denotes statistical significance between groups.

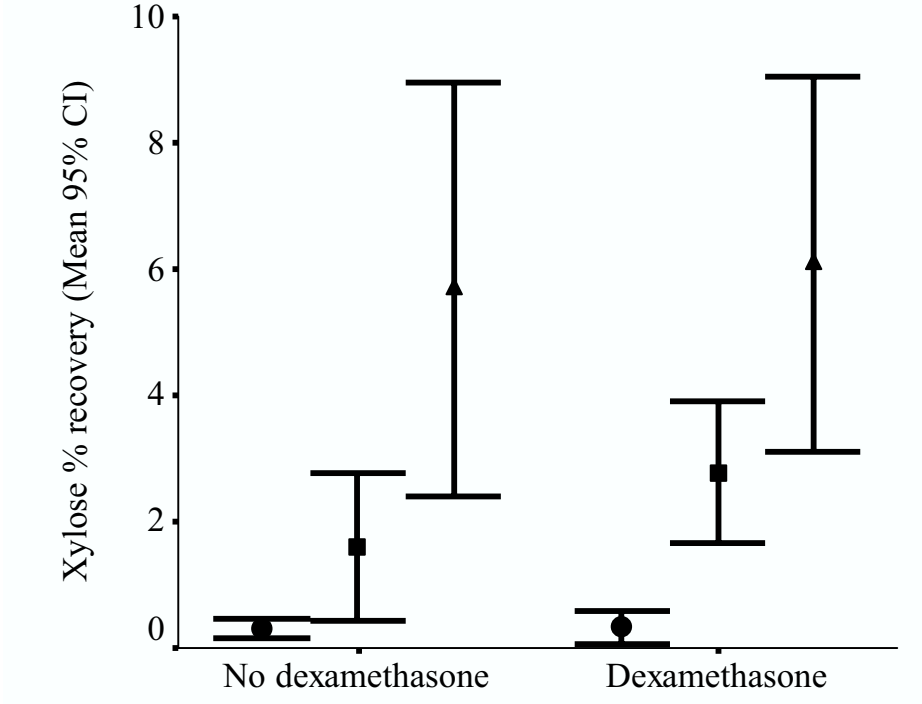

Fig 4: Changes of D-xylose percentage recovery in both groups. Values expressed as mean 95% CI. (●) T0, (■) T12, (▲) T24.* Denotes statistical significance between groups.

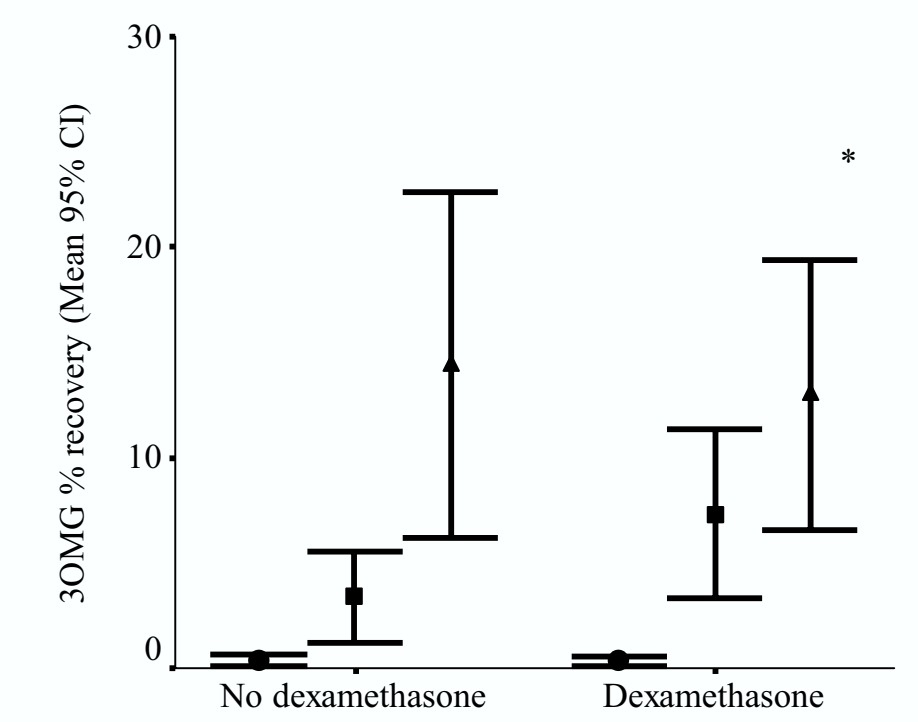

Fig 5: Changes of 3-O-D-Methyl-Glucose percentage recovery. Values expressed as mean 95% CI. (●) T0, (■) T12, (▲) T24.* Denotes statistical significance between groups.

Discussion

We have shown in this study that dexamethasone given before cardiopulmonary bypass starts reduces postoperative gut permeability as assessed by the DSPT. There was an age and weight difference between the two groups. This could be seen as a limiting factor in the interpretation of the results. Univariate analysis showed that both variables did not influence either L/R ratios or percentage recovery of the other two 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 healthy children; range 0.023 – 0.074 and mean (SD) 0.047 (0.018).[6]

Gut permeability has been investigated in adult patients undergoing coronary artery bypass surgery.[17] L/R ratios increased immediately after surgery returning to normal approximately 48 h after the surgical procedure. The DSPT has also been used to test the beneficial effects of dopexamine over dopamine in the splanchnic 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 non-cooperative patients without a urinary catheter. A high percentage of patients are discharged to the ward the day after surgery with the 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.[19,20] In an animal model it was shown that fluid loading increased the L/R ratios independent of changes in intestinal permeability. Rats received in an 8-hour period a fluid bolus equivalent to twice the daily fluid oral intake. Put into perspective, this means an infant of 10 kg would receive in an 8-hour period approximately 2 litres fluid intravenously. 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, intestinal transient 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 may be influenced not only by the permeability of the intestinal mucosa but also by pre and postabsorption factors. D-xylose and 3-O-methyl-D-glucose provide information about the functional state of the intestinal mucosa while the L/R ratio is a reflection of the mucosal integrity at the morphological level. Percentage recoveries for D-xylose and 3-O-methyl-D-glucose did not differ substantially between the two groups.

There is a trend towards 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 morphological level in our patients. However we have no explanation as to why dexamethasone did not affect the intestinal barrier at the functional level. A L/R ratio of 0.46 is nearly ten times the normal value and is a reflection of a highly permeable intestinal mucosa. If 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 diagnosed with 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 CPB starts. This has been demonstrated consistently by a number of studies.[23,11] Several cytokines, including interleukin 1 (IL-1), IL-4, IL-6, IL-10, interferon γ (IFN-γ), and tumour necrosis factor, have been reported to increase intestinal permeability in vitro.[3] IL-6 in particular may be a mediator of intestinal mucosal injury in various conditions associated with transient mesenteric hypoperfusion and subsequent inflammation.[24]

A combined administration of steroids hours before the operation plus its addition to the pump prime appears to be more beneficial.[25] Giving 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 anaesthesia only in patients undergoing a period of circulatory arrest.

The results of the present study are an encouragement to investigate if adding steroids to the pump prime may provide a better and/or faster improvement in gut permeability. Nevertheless the use of dexamethasone in paediatric cardiac surgery remains a controversial issue. Lindberg and colleagues[26] stated that omitting the use of dexamethasone in children weighing less than 10 Kg scheduled for cardiac surgery is unethical. Schroeder and colleagues[25] 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 developed gastrointestinal complications in the postoperative period and the clinical parameters measured were not affected by dexamethasone.

Using dexamethasone to improve intestinal function is not a new concept. As early as 1984, Bauer and colleagues noticed a reduction in the incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy.[27] Animal models have shown repeatedly that in the immature animal dexamethasone reduces bacterial translocation in the gut and increases the length of the small intestine.[28] The use of dexamethasone (0.5 to 1 mg kg^{-1} per day for several days) to treat or prevent chronic lung disease in preterm infants is discouraged after intensive review of the literature.[29] Our patients were not premature, were exposed to enteral feeding, and their intestinal wall was far from immature.

The mechanisms by which dexamethasone exerts its effects in the intestinal mucosa are not totally elucidated. Further research may be necessary.

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References

1. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology.* 2002;**97**:215-52.
2. Brix-Christensen V. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. *Acta Anaesthesiol Scand.* 2001;**45**:671-9.
3. Colgan SP, Parkos CA, Matthews JB, D'Andrea L, Awtrey CS, Lichtman AH, et al. Interferon-gamma induces a cell surface phenotype switch on T84 intestinal epithelial cells. *Am J Physiol.* 1994;**267**:C402-10.
4. Madsen KL, Lewis SA, Tavernini MM, Hibbard J, Fedorak RN. Interleukin 10 prevents cytokine-induced disruption of T84 monolayer barrier integrity and limits chloride secretion. *Gastroenterology.* 1997;**113**:151-9.
5. Beach RC, Menzies IS, Clayden GS, Scopes JW. Gastrointestinal permeability changes in the preterm neonate. *Arch Dis Child.* 1982;**57**:141-5.
6.Miki K, Butler R, Moore D, Davidson G. Rapid and simultaneous quantification of rhamnose, mannitol and lactulose by HPLC for estimating intestinal permeability in paediatric practice. *Clin Chem.* 1996;**42**:71-5.
7. Taylor RM, Bjarnason I, Cheeseman P, Davenport M, Baker AJ, Mieli-Vergani G, et al. Intestinal permeability and absorptive capacity in children with portal hypertension. *Scand J Gastroenterol.* 2002;**37**:807-11.
8. Malagon I, Onkenhout W, Klok G, van der Poel PF, Bovill JG, Hazekamp MG. Gut permeability in paediatric cardiac surgery. *Br J Anaesth* 2005;**94**:181-5.
9. Hebra A, Brown MF, Hirshl RB, McGeehin K, O'Neill JA Jr, Norwood WI, et al. Mesenteric ischemia in hypoplastic left heart syndrome. *J Pediatr Surg* 1993;**28**:606-11.
10. Chaney MA. Corticosteroids and cardiopulmonary bypass. A review of clinical investigations. *Chest.* 2002;**121**:921-31.
11. Bronicki RA, Backer CL, Baden HP, Mavroudis C, Crawford SE, Green TP. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg.* 2000;**69**:1490-5.
12. Schurr UP, Zund G, Hoerstrup SP, Grunenfelder J, Maly FE, Vogt PR, et al. Preoperative administration of steroids: Influence on adhesion molecules and cytokines after cardiopulmonary bypass. *Ann Thorac Surg.* 2000;**72**:1316-20.
13. Chaney MA, Durazo-Arvizu RA, Nikolov MP, Blakeman BP, Bakhos M. Methylprednisolone does not benefit patients undergoing coronary artery bypass grafting and early tracheal extubation. *J Thorac Cardiovasc Surg*:2001;**121**:561-9.

14. Onkenhout W, Groener JE, Verhoeven NM, Yin C, Laan LA. L-Arabinosuria: a new defect in human pentose metabolism. *Mol Genet Metab*. 2002;**77**:80-5.
15. Jansen G, Muskiet FA, Schierbeek H, Berger R, van der Slik W. Capillary gas chromatographic profiling of urinary, plasma and erythrocyte sugars and polyols as their trimethylsilyl derivatives, preceded by a simple and rapid prepurification method. *Clin Chim Acta.* 1986;**157**:277-94.
16. Shore S, Nelson DP, Pearl JM, Manning PB, Wong H, Shanley TP, et al. Usefulness of corticosteroid therapy in decreasing epinephrine requirements in critically ill infants with congenital heart disease. *Am J Cardiol.* 2001;**88**:591-4.
17. Ohri SK, Bjarnason I, Pathi V, Somasundaram S, Bowles CT, Keogh BE, et al. Cardiopulmonary bypass impairs small intestinal transport and increases gut permeability. *Ann Thorac Sur.* 1993;**55**:1080-6.
18. Sinclair DG, Houldsworth PE, Keogh B, Pepper J, Evans TW. Gastrointestinal permeability following cardiopulmonary bypass: a randomised study comparing the effects of dopamine and dopexamine. *Intensive Care Med.* 1997;**23**:510-6.
19. Hellemeesch MM, Lamers WH, Soeters PB, Deutz EP. Increased lactulose/rhamnose ratio during fluid load is caused by increased urinary lactulose excretion. *Am J Physiol Gastrointest Liver Physiol.* 2000;**278**:G83-8.
20. Fink MP. Interpreting dual-sugar absorption studies in critically ill patients; what are the implications of apparent increase in intestinal permeability to hydrophilic solutes? *Intensive Care Med.* 1997;**23**:489-92.
21. Menzies IS. Transmucosal passage of inert molecules in health and disease. In: Skadhauge E, Heinze K, eds. Intestinal absorption and secretion. London: MTP Press, 1983; 527-43.
22. Piena-Spoel M, Albers MJIJ, Kate J, Tibboel D. Intestinal permeability in newborns with necrotizing enterocolitis and controls: does the sugar absorption test provide guidelines for the time to (re-)introduce enteral nutrition? *J Pediatr Surg*. 2001;**36**:587-92.
23. Butler J, Pathi VL, Paton RD, Logan RW, MacArthur KJD, Jamieson MPG, et al. Acute-Phase response to cardiopulmonary bypass in children weighing less than 10 kilograms. *Ann Thorac Surg*. 1996;**62**:538-42.
24. Wang Q, Fang CH, Hasselgren PO. Intestinal permeability is reduced and IL-10 levels are increased in septic IL-6 knockout mice. *Am J Physiol Regul Integr Comp Physiol*. 2001;**281**:R1013-23.
25. Schroeder VA, Pearl JM, Schwartz SM, Shanley TP, Manning PB, Nelson DP. Combined steroid treatment for congenital heart surgery improves oxygen delivery and reduces postbypass inflammatory mediator expression. *Circulation*. 2003;**107**:2823-8.
26. Lindberg L, Forsell C, Jogi P, Olsson AK. Effects of dexamethasone on clinical course, C-reactive protein, S110B protein and von Willebrand factor antigen after paediatric cardiac surgery. *Br J Anaesth*. 2003;**90**:728-32.
27. Bauer CR, Morrison JC, Poole WK, Korones SB, Boehm JJ, Rigatto H, et al. A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. *Pediatrics*. 1984;**73**:682-8.
28. Wenzl HH, Schimpl G, Feierl G, Steinwender G. Effect of prenatal cortisone on spontaneous bacterial translocation from gastrointestinal tract in neonatal rat. *Dig Dis Sic*. 2003;**48**:1171-6.
29. Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics.* 2002;**109**:330-8.