Gut permeability and myocardial damage in paediatric cardiac surgery

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CHAPTER 7

Effect of dexamethasone on postoperative cardiac troponin T production in paediatric cardiac surgery

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Objectives: Paediatric cardiac surgery is associated with a temporary rise in cardiac troponin T (cTnT) during the postoperative period. We have tested the hypothesis that dexamethasone given before cardiopulmonary bypass starts may have myocardial protective effects as assessed by the postoperative production of cTnT.

Design: Prospective randomized interventional study.

Setting: Paediatric intensive care unit in a university hospital.

Interventions: Patients were randomly allocated to act as controls or receive a single dose of dexamethasone (1 mg kg^{-1}) during induction of anaesthesia.
Measurements and results: cTnT was measured four times postoperatively; immediately after admission to the paediatric intensive care unit (PICU) and at 8, 15 and 24 h thereafter. Both groups had similar cTnT concentrations on PICU admission; 2 (1.56 – 2.51) ng ml^{-1} (mean (95% Confidence Intervals)) in the group without dexamethasone and 1.85 (1.55 – 2.15) ng ml^{-1} in the group with dexamethasone. Concentrations of cTnT 8 h after admission to the PICU were 3.08 (2.46 – 3.69) ng ml^{-1} in patients not receiving dexamethasone and 1.99 (1.53 – 2.45) ng ml^{-1} in patients receiving dexamethasone. Overall differences between the two groups were significant ($P < 0.035$). After subgroup statistical analysis differences between the two groups remained significant only at 8 h ($P < 0.005$). At 15 h and 24 h after admission to the PICU differences were no longer significant.

Conclusions: The use of dexamethasone (1 mg kg^{-1}) before cardiopulmonary bypass starts is associated with a short lived significant reduction in postoperative cTnT production. The clinical significance of this effect is unclear.

The use of cardiopulmonary bypass (CPB) can induce a systemic inflammatory response syndrome in the postoperative period. This phenomenon is probably more exaggerated in the paediatric population as a greater proportion of the patient's blood is exposed to the surface of the CPB circuit.[1] The proinflammatory response associated with the use of CPB in children has been reviewed extensively elsewhere.[2] Within the paediatric population, neonates may react differently to CPB exposure, with higher proinflammatory cytokine production.[3]

Corticosteroids have been used extensively in adult cardiac surgery. Patients given methylprednisolone before CPB started had higher cardiac indices than those given placebo.[4] More recent studies, however, have shown that the use of methylprednisolone offered no clinical advantage in adults undergoing cardiac surgery with CPB.[5] Experience with steroids in paediatric cardiac surgery, on the other hand, is limited. The assumption has always been that the paediatric myocardium is more resistant to hypoxia than the adult one. This may not be the case.[6]

Steroids given before CPB starts reduce significantly the postoperative production of proinflammatory cytokines in children[7] and may provide myocardial protection during cardiac surgery. The use of troponins as surrogate markers to assess the potential myocardial protective effect of steroids is not a new concept.[8,9] However in those studies the investigators measured cardiac troponin I (cTnI). Sasse and colleagues[10] showed that up to nine months after birth in healthy infants, and for up to two years in infants with congenital heart disease, cTnI is not expressed solely in the myocardium, but is also expressed in variable amounts from slow twitch skeletal muscle.

Cardiac troponin T (cTnT) is a specific marker of myocardial infarction.[11] It is also a reliable marker of myocardial injury in children. Cardiac troponin T (cTnT) concentrations rise postoperatively in paediatric patients undergoing cardiac surgery with CPB;[12] up to three times the average cTnT that could be found in adult patients undergoing coronary artery bypass surgery.[13]

We have tested the hypothesis that dexamethasone given before CPB starts may have myocardial protective effects as assessed by the postoperative production of cTnT, the inotropic support and ventilator hours necessary after surgery. Subgroup analysis in cyanotic and neonatal patients was also evaluated for the same hypothesis. This study has been presented in part at a recent international meeting.[14]

Materials and Methods

After approval by the hospital ethics committee and parental consent 140 patients were prospectively investigated. This study was conducted between October 2003 and December 2004. Approximately 300 paediatric patients per year undergo cardiac surgical procedures in our institution. Patients operated without CPB were not recruited. cTnT was measured four times during the first 24 h following admission to the paediatric intensive care unit (PICU). This is standard practice in our institution. Patients were randomized using standard randomization tables 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 hospital ethics committee. We used a process of minimization to achieve similar number of patients for each surgical procedure. The first patient for each operation was allocated at random. For each subsequent patient we determined which treatment would lead to a better balance between the groups with respect to the type of operation. The patient was then randomized using a weighting system in favour of the treatment which would minimize the imbalance.[15] cTnT concentrations were measured by the hospital clinical chemistry laboratory, and the analysts were unaware of the conduct of this study.

The anaesthetic technique was similar for both groups. 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 either midazolam (0.2 mg kg^{-1} h^{-1}) or propofol (6 mg kg^{-1} h^{-1}), and sufentanil (2 μg kg^{-1} h^{-1}). The lungs of the patients were ventilated with oxygen/air (F_IO_2 = 0.5). Ventilation was discontinued during CPB. After heparin administration (3 mg kg^{-1} or 300 IU 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, 325 to 750 ml according to the patient's weight, contained lactate-free Ringer's solution, albumin, mannitol, blood and heparin. Body temperature during bypass was maintained at 28 °C except for patients undergoing circulatory arrest, who were cooled to 20 °C during the period of circulatory arrest. Patients underwent modified ultrafiltration at the end of the bypass. The amount of fluid ultrafiltered was 60 (49 – 63) ml kg^{-1} (mean 95% Confidence Intervals).

In the PICU, patients were sedated with a combination of midazolam (0.1 -0.2 mg kg^{-1} h^{-1}) and morphine (10-20 μg kg^{-1} h^{-1}). Our practice is not to use diuretics in the first 24 h after admission to the PICU.

Blood samples (0.5 ml) were taken for measurement of cTnT concentrations immediately after admission to the paediatric intensive care unit (PICU), and 8, 15 and 24 h after admission. Samples were collected in a Gel-Microtainer tube and immediately analysed using the Elecsys Modular E170 immunochemistry analyzer (Cardiac Troponin T, Roche Diagnostics, Mannheim, Germany). Briefly, this immunoassay employs two monoclonal antibodies specifically directed against human cardiac troponin T. The antibodies recognize two epitopes located in the central part of the cardiac troponin T protein. The lower detection limit is 0.01 ng ml^{-1}. Ten patients admitted to the PICU before surgery had preoperative cTnT concentrations measured as part of standard clinical practice.

Arterial oxygen tension (PaO_2), pH, base excess (BE), bicarbonate and lactate were recorded immediately after admission to the intensive care unit and 24 h later (Chiron 865, Bayer, Mijdrecht, The Netherlands). Ventilator hours were also recorded.

The type and amount of vasoactive drugs were recorded after admission to the PICU 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). Fluid intake (including crystalloids, colloids and blood products), output (urine, blood and serous fluid loss) and fluid balance were recorded over a 36 h period following admission to the PICU.

Statistical analysis

In a retrospective analysis of fifteen paediatric patients who had undergone cardiac surgery the mean (SD) cTnT concentration postoperatively was 1.92 (2.13) ng ml^{-1}. A power analysis based on these findings showed that we would need 90 patients to detect a difference in cTnT of 2 ng ml^{-1} with = 0.05 and a power of 95%. In the same retrospective analysis the mean (SD) ventilator hours was 64 (37) hours and more than 50% of the patients needed two or more inotropic drugs postoperatively.

A power analysis based on these findings showed that we would need 136 patients to detect a reduction of 18 h in ventilation time and 130 patients to detect a 50% reduction on inotropic support. These two variables with = 0.05 and a power of 80%.

Data were analysed with the statistical package SPSS v10, and are summarized as mean and 95% confidence intervals. Patient characteristics (age, weight, surgery times and ventilator hours), fluid balance and blood gas variables were analyzed with unpaired t test for normally distributed data and Mann-Whitney test for non-normally distributed data. Because cTnT concentrations were not normally distributed, the data were first subjected to a natural logarithmic transformation before analysis by repeated measures ANOVA with the Greenhouse-Geisser correction. Categorical data were analyzed using the Chi-squared test. Correlation coefficients between variables were calculated using Pearson test for normally distributed data and Spearman test for non normally distributed data. Values of $P < 0.05$ were considered statistically significant. Data are presented as mean (95% Confidence Intervals).

Results

The groups were comparable with respect to age, sex, weight, surgery times, aortic cross-clamp, bypass and arrest times (Table 1). The number of cyanotic patients and those who underwent a ventriculotomy were similar in both groups. There were no statistically significant differences between the groups with regards to ventilator hours, PaO_2/FiO_2 ratios, and lactate. PaO_2/FiO_2 ratios did not change significantly when values from acyanotic and cyanotic patients were analyzed separately. Fluid intake did not differ between the groups throughout the study period, although the positive balance in the patients receiving dexamethasone was significantly less during the first postoperative day. During day two there were no differences between the two groups in terms of fluid intake, output and total fluid balance. Table 2 shows the type of operations performed in each group. Table 3 shows the type of operations performed in neonates while table 4 shows the type of operations performed in cyanotic patients. In the 10 patients from whom blood samples were obtained preoperatively, cTnT concentrations were less than 0.02 ng ml^{-1}.

Differences between the two groups were statistically significant ($p < 0.035$). Both groups had comparable cTnT concentrations on PICU admission (T0); 2 (1.56 – 2.51) ng ml^{-1} in the group without dexamethasone and 1.8 (1.54 – 2.14) ng ml^{-1} in the group given dexamethasone.

	No dexamethasone	Dexamethasone
Number of patients	70	70
Age (months)	12.8 (6.4 – 19.3)	12.2 (6.7 – 17.8)
Sex (M/F)	33/37	43/27
Weight (kg)	7.3 (5.6 – 8.9)	6.4 (5.3 – 7.5)
Surgery time (min)	198 (184 – 212)	207 (188 – 226)
Bypass time (min)	124 (110 – 137)	127 (112 – 142)
Aortic clamp time (min)	78 (64 – 91)	72 (60 – 84)
Arrest time (min)	7.5 (2.1 – 12.8)	6.5 (2.7 – 10.3)
Ventriculotomy (Y/N)	20/50	16/54
Cyanotic (Y/N)	35/35	40/30
Ventilator hours	97 (74 – 119)	99 (76 – 122)
Inoscore day one	10 (8 – 13)	9 (6 – 12)
Inoscore day two	11 (8 – 14)	10 (8 – 13)
Fluid balance day one		
Intake (ml kg^{-1})	69 (62 – 77)	62 (55 – 69)
Output (ml kg^{-1})	34 (28 – 40)	37 (32 – 42)
Balance (ml kg^{-1})	35 (28 – 43)	25 (17 – 32)*
Fluid balance day two		
Intake (ml kg^{-1})	100 (86 – 114)	99 (88 – 110)
Output (ml kg^{-1})	73 (60 – 85)	80 (60 – 100)
Balance (ml kg^{-1})	27 (16 – 37)	18 (-2.5 – 39)
Lactate day one	1.98 (1.44 – 2.53)	1.59 (1.28 – 1.91)
Lactate day two	1.80 (1.58 – 2.02)	1.57 (1.40 – 1.74)
PaO_2/FiO_2 day one	41.8 (35.8 – 47.7)	36.6 (30.4 – 42.8)
PaO_2/FiO_2 day two	32.9 (27.9 – 38)	33.3 (27.8 – 38.7)

Table 1: Patient characteristics. Values expressed as mean (95% Confidence Intervals).* Denotes statistical significance.

However, subgroup analysis demonstrated that only at 8 h after admission, the cTnT concentrations were significantly higher ($p < 0.005$) in the non-dexamethasone group (3.1 (2.5 – 3.7) ng ml^{-1}) than in the dexamethasone group (1.9 (1.5 – 2.4) ng ml^{-1}). There were no significant differences in the cTnT concentrations between the groups at the other times. cTnT concentrations at T15 were 2.65 (2.12 – 3.19) ng ml^{-1} in the non-dexamethasone group and 1.95 (1.46 – 2.43) ng ml^{-1} in the dexamethasone group.

	No dexamethasone	Dexamethasone
AS	3	1
Atrial septation	1	
AVSD	7	6
Fontan	6	2
Glenn	5	10
Homograft	2	2
IAA	1	1
MAPCA	1	1
MVA	1	2
MVR	1	
Norwood	4	5
PS	1	1
Rastelli	1	1
Switch	10	10
TAPVC	2	3
ToF	9	9
Truncus	2	1
TVA		1
TVR	1	
VSD	12	14
Total	70	70

Table 2: Type of operations. Aortic stenosis (AS), Atrioventricular septal defect (AVSD), Interrupted aortic arch correction (IAA), Major aortopulmonary collateral arteries (MAPCA), Mitral valve anuloplasty (MVA), Mitral valve replacement (MVR), Pulmonary stenosis (PS), Total anomalous pulmonary venous connection (TAPVC), Tetralogy of Fallot (ToF),Tricuspid valve anuloplasty (TVA), Tricuspid valve replacement (TVR), Ventricular septal defect (VSD).

At T24 were 2.27 (1.77 – 2.76) ng ml^{-1} in the non-dexamethasone group and 1.81 (1.33 – 2.28) ng ml^{-1} in the dexamethasone group. Figure 1 is a graphical representation of the changes in cTnT concentrations in the two groups. Figure 2 and 3 show changes in cTnT concentrations in cyanotic and neonatal patients respectively. Correlation between cTnT concentrations at T8 and ventilator hours was significant although weak. Correlation coefficient was $r = 0.40$ in patients not receiving dexamethasone and $r = 0.49$ in those receiving dexamethasone.

	No dexamethasone	Dexamethasone
Homograft		1
IAA	1	1
MAPCA	1	
MVR	1	
Norwood	4	5
Switch	8	8
TAPVC	1	1
Truncus	1	1
VSD	2	1
Total	19	18

Table 3: Type of operation in neonatal patients. Interrupted aortic arch correction (IAA), Major aortopulmonary collateral arteries (MAPCA), Mitral valve replacement (MVR), Total anomalous pulmonary venous connection (TAPVC).

	No dexamethasone	Dexamethasone
Fontan	6	2
Glenn	5	10
Homograft		1
MAPCA	1	1
Norwood	4	5
Rastelli	1	1
Switch	10	10
TAPVC		2
ToF	8	7
TVA		1
Total	35	40

Table 4: Type of operation in cyanotic patients. Major aortopulmonary collateral arteries (MAPCA). Total anomalous pulmonary venous connection (TAPVC). Tetralogy of Fallot (ToF). Tricuspid valve anuloplasty (TVA).

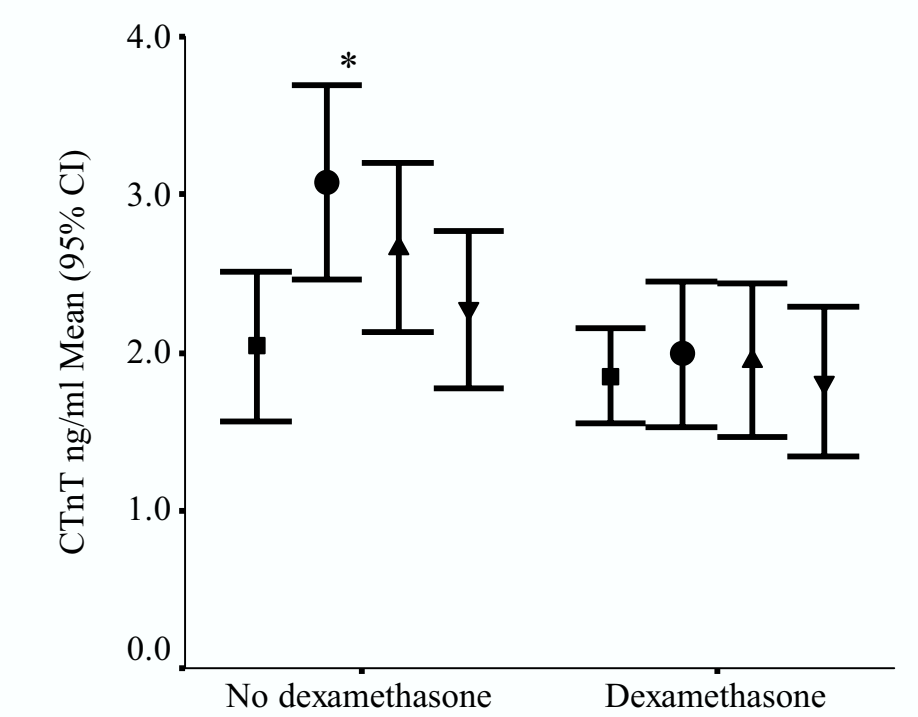

Fig 1: Changes in cTnT concentrations during the first 24 h after operation. (■) T0, (●) T8, (▲) T15 and (▼) T24.Values expressed as mean (95% Confidence Intervals). * Denotes statistical significance at that time point between the two groups.

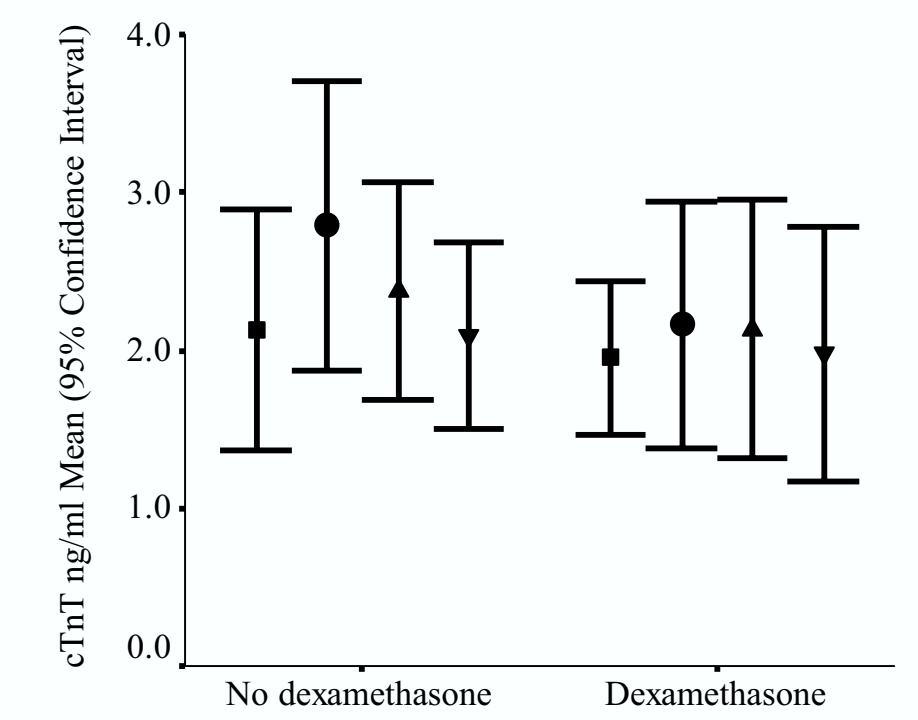

Fig 2: Changes in cTnT concentrations during the first 24 h after operation in cyanotic patients. (■) T0, (●) T8, (▲) T15 and (▼) T24. Differences are not significant.

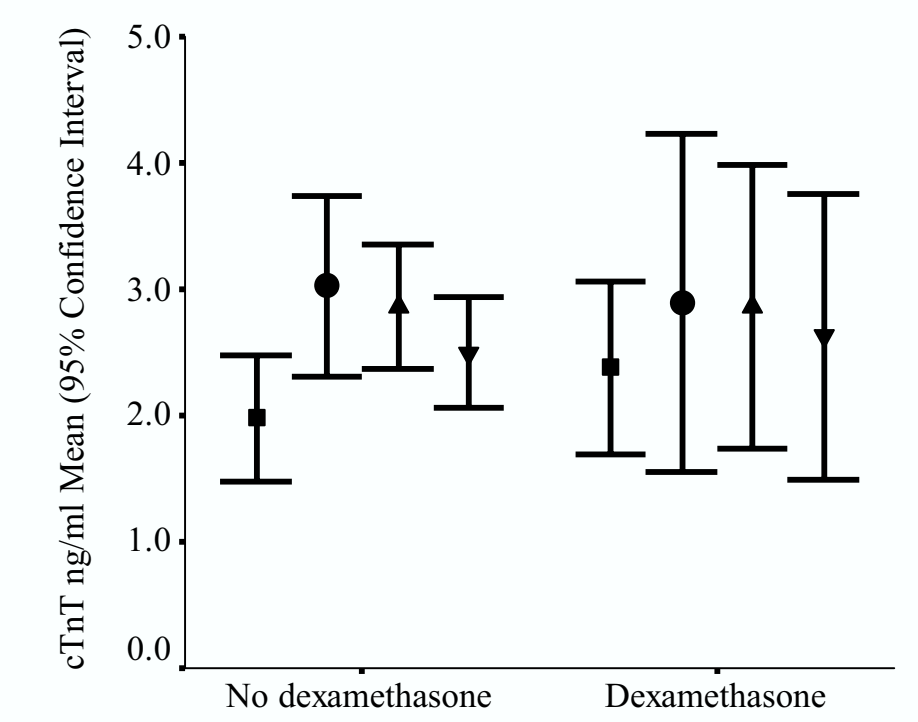

Fig 3: Changes in cTnT concentrations during the first 24 h after operation in neonatal patients. (■) T0, (●) T8, (▲) T15 and (▼) T24. Differences are not significant.

When both groups were analyzed together the correlation coefficient was r = 0.45. Correlations between cTnT concentrations (T8) and inotropic scores at admission and 24 h later were also weak in both groups; no dexamethasone group r = 0.38 (admission inotropic scores) and r = 0.51 (inotropic scores 24 h). In the dexamethasone group correlations were r = 0.29 (admission inotropic scores) and r = 0.55 (inotropic scores 24 h).

Discussion

The systemic inflammatory response syndrome following CPB has been implicated in myocardial injury leading to low cardiac output and increased inotropic requirements in the postoperative period.[16] One of the strategies aimed at protecting the myocardium is the use of steroids before CPB starts. We have shown in the present study that while dexamethasone reduces the postoperative production of cTnT in paediatric cardiac surgery, its effects are short lived. Fifteen hours after the end of the surgical procedure, there are no statistically significant differences between the dexamethasone and the control group.

The concentrations of cTnT found in our study are in line with what it has been reported in other studies. Immer and colleagues[12,17] reported mean cTnT concentrations of 4.06 ng ml^{-1} and 5.5 ng ml^{-1} in two consecutive studies with a patient population similar to ours. A mean concentration of 5 ng ml^{-1} was reported in neonates with transposition of the great arteries undergoing arterial switch operation with circulatory arrest.[18]

Checchia and colleagues[8] investigated the effect of dexamethasone (1 mg kg^{-1}) on the postoperative production of cTnI in 28 paediatric patients undergoing cardiac surgery with CPB. They found a statistically significant reduction in cTnI concentrations 24 h after surgery in patients who received dexamethasone compared to those given a placebo. In our study we did not find any difference on the cTnT concentrations 24 h after the surgical procedure between the two groups. Other investigators have found that cTnT peaked at 4 hours after CPB,[18] 30 minutes after CPB[20] and 2 hours after declamping.[21] It is not clear why cTnT concentrations peaked 8 h after admission to the PICU in our patients.

A beneficial effect of steroids on cTnI degradation has been demonstrated.[9] However this study was performed in animals subjected to a 2 h period of deep hypothermic circulatory arrest (DHCA) and methylprednisolone was given twice, 6 h before and immediately before CPB started.

Imura and colleagues[19] showed an age-dependent and hypoxia-related difference in myocardial injury during CPB. Other investigators[20] have also noted that cyanotic patients have higher cTnT concentrations postoperatively than the acyanotic counterparts. Reperfusion injury may explain this phenomenon. When CPB starts cyanotic patients are suddenly exposed to normoxic concentrations of oxygen. According to our results, cyanotic patients do not shown any improvement in the postoperative production of cTnT when dexamethasone is used.

The neonate myocardium has a distinct systemic inflammatory response to CPB, with higher production of proinflammatory cytokines when compared to older patients.[3] We could not find any improvement in cTnT production in neonates treated with dexamethasone. Bronicki and colleagues[7] found a significant reduction on postoperative fluid requirements in the paediatric cardiac surgical patients (n = 15) who received dexamethasone compared to the placebo group (n = 14). The timing and amount of dexamethasone was similar to our study design.

Fluid balance in the first postoperative day is significantly less in the dexamethasone group. However we consider this difference not clinically relevant. Fluid balance in the dexamethasone group on day one and the no dexamethasone group on day two are similar.

The use of steroids in adult cardiac surgery remains controversial.[5] To our knowledge there are no prospective or retrospective cohort studies that clearly show the influence of steroids on the clinical postoperative course. Nevertheless the use of steroids in paediatric cardiac surgery has become accepted practice in many institutions. Lindberg and colleagues[22] consider that omitting the use of dexamethasone in children weighing less than 10 kg scheduled for cardiac surgery is unethical.

Dexamethasone reduces C-reactive protein production without any effect on the release of protein S100B and Von Willebrand factor.[22] The concentration of proinflammatory cytokines decreases when steroids are used before CPB starts.[7,24] The reduction is even more pronounced if steroids are given before and during CPB.[23] Oxygen delivery and cardiac output improve faster when steroids were used in an animal model.[25] Steroids may not exert their effects through anti-inflammatory properties but by up-regulation of calpastatin,[9] a protein that prevents the degradation of cTnI at the intracellular level. Even the timing of steroid administration seems to be relevant.[26]

However when clinical end points have been used to test the benefits of steroids the results are not so impressive.[27] Our study was powered to detect a 50% reduction on inotropic support or an 18 h reduction in ventilator hours. For these targets we had to include 68 patients in each group. Our results however show that the use of dexamethasone was not associated with any significant improvement in the postoperative use of inotropic drugs, fluid requirements, lactate production, ventilator hours or PaO_2/FiO_2 ratios. Some concerns have been raised regarding the use of cTnT in patients with chronic renal failure.[28] None of the patients included in the study had either acute or chronic renal failure during the study period. Some studies have suggested that cTnT concentrations may be used as prognostic indicators of postoperative recovery.[17,18] In our study ventilator hours and inotropic scores correlated with cTnT production. However, although statistically significant the correlations were weak.

The present study has a number of limitations. We did not investigate cardiac function parameters (shortening fraction, ejection fraction) and its relationship with cTnT elevations in the postoperative period. Atriotomy[29] and ventriculotomy[30] influence cTnI production independent of myocardial damage related to other factors. The number of patients undergoing atriotomy was similar in both groups ($p < 1$) and therefore unlikely to influence the results.
More patients required a ventriculotomy in the control group ($n = 20$) than in the dexamethasone group ($n = 16$). While the difference is not significant ($p < 0.56$) it could have affected the results.

Ventilator hours in our study appear unacceptably high at first glance. However, some of the patients included in this study are known to have prolonged postoperative course (i.e. HLHS, TAPVC, Truncus arteriousus, etc.) while in the majority of patients (i.e. VSD, AVSD, ToF, TGA, valve surgery, Glenn, Fontan, etc.) extubation within 24 to 48 h is standard of care. The use of the mean as statistical instrument to describe the population may have interfered with these results. Power analysis for ventilator hours and inotropic support were based on average retrospective values from our intensive care unit.

In conclusion, this study has demonstrated that in paediatric patients undergoing cardiac surgery the use of dexamethasone given before CPB starts is associated with a significant albeit short lived reduction in postoperative production of cTnT. Subgroup analysis showed that dexamethasone did not improve postoperative production of cTnT neither in cyanotic nor in neonatal patients.

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