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

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Abstract *Objective:* Pediatric cardiac surgery is associated with a temporary rise in cardiac troponin T (cTnT) during the postoperative period. We examined whether dexamethasone given before cardiopulmonary bypass has myocardial protective effects as assessed by the postoperative production of cTnT. *Design and setting:* Prospective randomized interventional study in the pediatric 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) during induction of anesthesia. *Measurements and results:* cTnT was measured four times postoperatively: immediately after admission to the pediatric intensive care unit (PICU) and 8, 15, and 24 h thereafter. The two groups had similar mean cTnT concentrations on PICU admission: those receiving dexamethasone 1.85 ng/ml (1.55–2.15) and those not receiving it 2 ng/ml (95% confidence interval 1.56–2.51). Concentrations of cTnT 8 h after admission to the PICU differed significantly after 8 h: 1.99 ng/ml (1.53–2.45) in those receiving dexamethasone and 3.08 ng/ml (2.46–3.69) in those not receiving it. After subgroup statistical analysis differences between the two groups remained significant only at 8 h, not those after 15 or 24 h. *Conclusions:* The use of dexamethasone (1 mg/kg) before cardiopulmonary bypass is associated with a brief but significant reduction in postoperative cTnT production. The clinical significance of this effect is unclear.

Keywords Cardiac surgery · Pediatric · Dexamethasone · Troponin T

Introduction

The use of cardiopulmonary bypass (CPB) can induce a systemic inflammatory response syndrome in the postoperative period. This phenomenon is probably more pronounced in the pediatric 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 pediatric 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 have higher cardiac indices than those given placebo [4]. More recent studies have shown no clinical advantage of methylprednisolone in adults undergoing cardiac surgery with CPB [5]. Experience with steroids in pediatric cardiac surgery is limited. The pediatric myocardium has traditionally been thought more resistant to hypoxia than the adult one. However, this may not be the case [6].

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

	No dexamethasone (n=70)	Dexamethasone (n=70)	p
Age (months)	12.8 (6.4–19.3)	12.2 (6.7–17.8)	0.88
Sex: M/F	33/37	43/27	0.12
Weight (kg)	7.3 (5.6–8.9)	6.4 (5.3–7.5)	0.38
Surgery time (min)	198 (184–212)	207 (188–226)	0.43
Bypass time (min)	124 (110–137)	127 (112–142)	0.74
Aortic clamp time (min)	78 (64–91)	72 (60–84)	0.51
Arrest time (min)	7.5 (2.1–12.8)	6.5 (2.7–10.3)	0.76
Atriotomy: Y/N	54/16	55/15	1
Ventriculotomy: Y/N	20/50	16/54	0.56
Cyanotic: Y/N	35/35	40/30	0.49
Ventilator duration (h)	97 (74–119)	99 (76–122)	0.87
Inoscore day 1	10 (8–13)	9 (6–12)	0.45
Inoscore day 2	11 (8–14)	10 (8–13)	0.54
Fluid balance day 1			
Intake (ml/kg)	69 (62–77)	62 (55–69)	0.78
Output (ml/kg)	34 (28–40)	37 (32–42)	0.47
Balance (ml/kg)	35 (28–43)	25 (17–32)*	0.02
Fluid balance day 2			
Intake (ml/kg)	100 (86–114)	99 (88–110)	0.95
Output (ml/kg)	73 (60–85)	80 (60–100)	0.51
Balance (ml/kg)	27 (16–37)	18 (−2.5 to 39)	0.48
Lactate day 1 (mmol/l)	1.98 (1.44–2.53)	1.59 (1.28–1.91)	0.21
Lactate day 2 (mmol/l)	1.80 (1.58–2.02)	1.57 (1.40–1.74)	0.08
PaO_2/FIO_2 day 1	41.8 (35.8–47.7)	36.6 (30.4–42.8)	0.3
PaO_2/FIO_2 day 2wo	32.9 (27.9–38)	33.3 (27.8–38.7)	0.77

* $p \leq 0.05$

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 9 months after birth in healthy infants, and for up to 2 years in infants with congenital heart disease, cTnI is not expressed solely in the myocardium but also 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. cTnT concentrations rise postoperatively in pediatric patients undergoing cardiac surgery with CPB [12]: up to three times the average cTnT in adult patients undergoing coronary artery bypass surgery [13].

We tested the hypothesis that dexamethasone given before CPB has myocardial protective effects as assessed by the postoperative production of cTnT, inotropic support, and ventilator duration necessary after surgery. Subgroup analysis in cyanotic and neonatal patients was also carried out. The findings have 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 pediatric patients per year undergo cardiac surgical procedures in our institution. Patients operated on without CPB were not recruited. cTnT was measured four times during the first 24 h following admission to the pediatric 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) during induction of anesthesia 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 numbers 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 favor 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 groups were comparable with respect to age, sex, weight, surgery times, aortic cross-clamp, bypass, and arrest times (Table 1). The numbers of cyanotic patients and those who underwent a ventriculotomy were similar in the two. Table 2 presents the type of operations performed in each group, Table 3 those performed in neonates, and Table 4 those performed in cyanotic patients. In the 10 patients from whom blood samples were obtained preoperatively cTnT concentrations were less than 0.02 ng/ml.

The anesthetic technique was similar in each group. Patients received a premedication consisting on oral atropine (0.02 mg/kg) and midazolam (0.5 mg/kg) 30 min before induction of anesthesia. Anesthesia was induced with sevoflurane followed by a bolus of sufentanil (1 μg/kg) and pancuronium (0.2 mg/kg). Maintenance of anesthesia consisted on a combined continuous infusion of either

Table 2 Type of operations. (*AS* aortic stenosis, *AVSD* atrioventricular septal defect, *IAA* interrupted aortic arch correction, *MAPCA, PA* major aortopulmonary collateral arteries plus pulmonary atresia, *MVA* mitral valve anuloplasty, *MVR* mitral valve replacement, *PS* pulmonary stenosis, *TAPVC* total anomalous pulmonary venous connection, ToF tetralogy of Fallot,*TVA* tricuspid valve anuloplasty, *TVR* tricuspid valve replacement, *VSD* ventricular septal defect)

	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, PA	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 3 Type of operation in neonatal patients (*IAA* interrupted aortic arch correction, *MAPCA, PA* major aortopulmonary collateral arteries plus pulmonary atresia, *MVR* mitral valve replacement, *TAPVC* total anomalous pulmonary venous connection)

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

midazolam (0.2 mg/kg per hour) or propofol (6 mg/kg per hour), and sufentanil (2 μg/kg per hour). The lungs of the patients were ventilated with oxygen/air (FIO_2=0.5). Ventilation was discontinued during CPB. After heparin administration (3 mg/kg or 300 IU/kg) and aorta cannulation CPB was instituted with a Dideco hollow fiber oxygenator with a blood flow between 200 and 300 ml/kg per minute. The prime volume, 325–750 ml depending on 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 in 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 mean amount of fluid ultrafiltered was 60 ml/kg (95% confidence interval 49–63). In the PICU patients were sedated with a combination of midazolam (0.1–0.2 mg/kg per hour) and morphine (10–20 μg/kg per hour). Our practice is not to use diuretics in the first 24 h after admission to the PICU.

Table 4 Type of operation in cyanotic patients (*MAPCA, PA* major aortopulmonary collateral arteries plus pulmonary atresia, *TAPVC* total anomalous pulmonary venous connection, *ToF* tetralogy of Fallot, *TVA* tricuspid valve anuloplasty)

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

Blood samples (0.5 ml) were taken for measurement of cTnT concentrations immediately after PICU admission and 8, 15, and 24 h thereafter. Samples were collected in a Gel-Microtainer tube and analyzed immediately 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 cTnT. The antibodies recognize two epitopes located in the central part of the cTnT protein. The lower detection limit is 0.01 ng/ml. 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 levels 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 supportinotrope 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. Values not differ between the groups throughout the study period, although the positive balance in the patients receiving dexamethasone was significantly less during postoperative day 1; during day 2 there were no differences between the two groups in terms of fluid intake, output, or total fluid balance.

Retrospective analysis of 15 pediatric patients who had undergone cardiac surgery revelaed a mean postoperative cTnT concentration of 1.92±2.13 ng/ml. A power analysis based on these findings showed that we would need 90 patients to detect a difference in cTnT of 2 ng/ml with α=0.05 and a power of 95%. In the same retrospective analysis the mean ventilator hours was 64±37 h, 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 α=0.05 and a power of 80%. Data were analyzed with the statistical package SPSS version 10 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 by the unpaired *t* test for normally distributed data and the Mann-Whitney test for nonnormally distributed data. Because cTnT concentrations were not normally distributed, the data were first subjected to a natural logarithmic transformation before analysis by

repeated-measures analysis of variance with the Greenhouse-Geisser correction. Categorical data were analyzed using the χ^2 test. Correlation coefficients between variables were calculated using Pearson's test for normally distributed data and Spearman's test for nonnormally distributed data. Differences at the level of $p<0.05$ were considered statistically significant. Data are presented as mean (95% confidence intervals).

Results

Differences between the two groups were statistically significant ($p<0.035$). The two groups had comparable cTnT concentrations on PICU admission: 2 ng/ml (1.56–2.51) in the group without dexamethasone and 1.8 (1.54–2.14) ng/ml in the group with. However, subgroup analysis demonstrated that only at 8 h after admission were the cTnT concentrations significantly higher ($p<0.005$) in the nondexamethasone group (3.1 ng/ml, 2.5–3.7) than in the dexamethasone group (1.9 ng/ml, 1.5–2.4). There were no significant differences in TnT concentrations between the groups at the other times. cTnT concentrations at T15 were 2.65 ng/ml (2.12–3.19) in the nondexamethasone group and 1.95 ng/ml (1.46–2.43) in the dexamethasone group. After 24 h values were 2.27 ng/ml (1.77–2.76) in the nondexamethasone group and 1.81 ng/ml (1.33–2.28) in the dexamethasone group. Figure 1 presents the changes in cTnT concentrations in the two groups. Figures 2 and 3 show changes in cTnT concentrations in cyanotic and neonatal patients, respectively.

The correlation between cTnT concentrations at 8 h and ventilator duration was significant although weak. The correlation coefficient was $r=0.40$ in those not receiving dexamethasone and $r=0.49$ in those receiving it; when the two groups were analyzed together the correlation coefficient was $r=0.45$. Correlations between cTnT concentrations (8 h) and inotropic scores at admission and 24 h later were also weak in both groups: in the nondexamethasone group $r=0.38$ (admission inotropic scores) and $r=0.51$ (inotropic scores 24 h), and in the dexamethasone group $r=0.29$ (admission inotropic scores) and $r=0.55$ (inotropic scores 24 h).

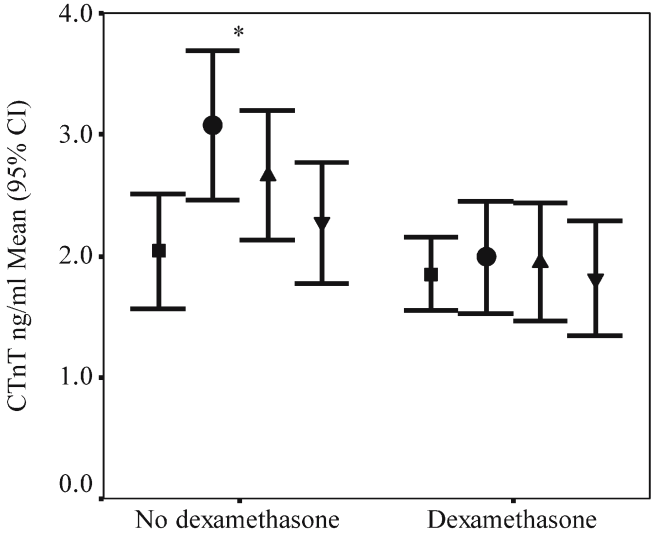

Fig. 1 Changes in cTnT concentrations during the first 24 h after operation: at admission (■) and after 8 h (●), 15 h (▲), and 24 h (▼). Means and 95% confidence intervals. *$p\leq0.05$ between the two groups

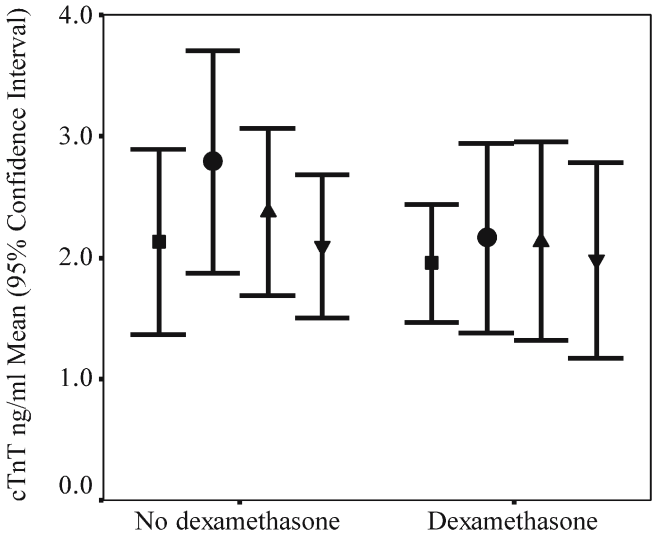

Fig. 2 Changes in cTnT concentrations during the first 24 h after operation in cyanotic patients: at admission (■) and after 8 h (●), 15 h (▲), and 24 h (▼). Means and 95% confidence intervals. Differences are not significant

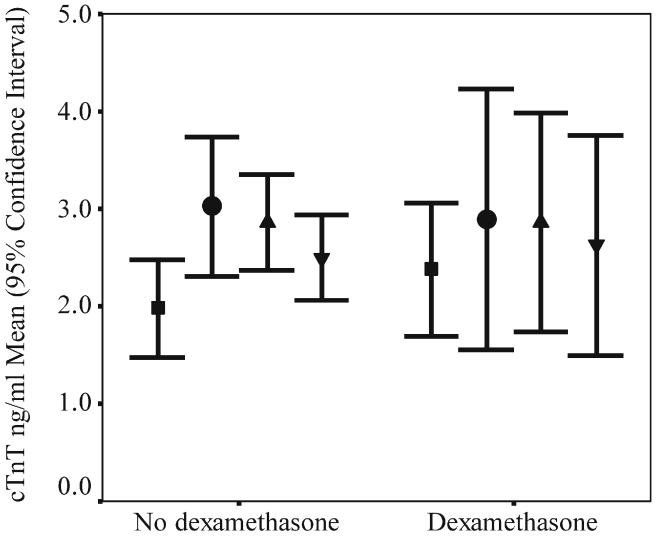

Fig. 3 Changes in cTnT concentrations during the first 24 h after operation in neonatal patients: at admission (■) and after 8 h (●), 15 h (▲), and 24 h (▼). Means and 95% confidence intervals

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 for protecting the myocardium is the use of steroids before CPB starts. The present study demonstrates that while dexamethasone reduces the postoperative production of cTnT in pediatric 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 that which has been reported in other studies. Immer and colleagues [12, 17] reported mean cTnT concentrations of 4.06 and 5.5 ng/ml in two consecutive studies with a patient population similar to ours. A mean concentration of 5 ng/ml 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) on the postoperative production of cTnI in 28 pediatric patients undergoing cardiac surgery with CPB. They found significantly lower cTnI concentrations 24 h after surgery in patients who received dexamethasone than in those given placebo. In our study we found no difference in cTnT concentrations 24 h after the surgical procedure between the two groups. Other investigators have found that cTnT peaked at 4 h after CPB [18], 30 min after CPB [19], and 2 h after declamping [20]. 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 2 h of deep hypothermic circulatory arrest and methylprednisolone was given twice, 6 h before and immediately before CPB started. Imura and colleagues [21] showed an age-dependent and hypoxia-related difference in myocardial injury during CPB. Other investigators [19] have also noted that cyanotic patients have higher cTnT concentrations postoperatively than the acyanotic counterparts. Reperfusion injury may explain this phenomenon. When CPB begins cyanotic patients are suddenly exposed to normoxic concentrations of oxygen. According to our findings, cyanotic patients show no 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 than older patients [3]. We found no improvement in cTnT production in neonates treated with dexamethasone. Bronicki and colleagues [7] reported significantly lower in postoperative fluid requirements among pediatric cardiac surgical patients (n=15) who received dexamethasone than in the placebo group (n=14). The timing and amount of dexamethasone was similar to those in our study design. Fluid balance in the first postoperative day was significantly less in the dexamethasone group. However, we do not consider this difference to be clinically relevant. Fluid balance in the dexamethasone group on day 1 and the no-dexamethasone group on day 2 were similar.

The use of steroids in adult cardiac surgery remains controversial [5]. To our knowledge, there are no prospective or retrospective cohort studies that show a clear effect of steroids on the clinical postoperative course. Nevertheless the use of steroids in pediatric 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 or von Willebrand factor [22]. The concentration of proinflammatory cytokines decreases when steroids are used before CPB begins [7, 23]. The reduction is even more pronounced if steroids are given before and during CPB [24]. Oxygen delivery and cardiac output improved more rapidly when steroids were used in an animal model [25]. Steroids may not exert their effects through anti-inflammatory properties but by upregulation 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 endpoints were used to test the benefits of steroids, the results are less impressive [27].

Our study was powered to detect a 50% reduction on inotropic support or an 18 h reduction in ventilator duration. For these targets we had to include 68 patients in each group. Our findings, 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 duration, or PaO_2/FIO_2 ratio. 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 can be used as prognostic indicators of postoperative recovery [17, 18]. In our study ventilator duration and inotropic scores were 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] affect cTnI production independent of myocardial damage related to other factors. The number of patients undergoing atriotomy was similar in the two groups (p<1) and therefore unlikely to affect 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 may have affected the results. Ventilator duration in our study appear unacceptably high at first glance. However, some of the patients included in this study were known to have prolonged postoperative course (e.g., hypoplastic left heart syndrome, total abnormal pulmonary venous return, truncus arteriousus) while in the majority of patients (e.g., ventricular septal defect, atrioventricular septal defect, tetralogy of Fallot, transposition of the great arteries, valve surgery, Glenn operation, Fontan operation) extubation within 24–48 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 demonstrates that in pediatric patients undergoing cardiac surgery the use of dexamethasone given before CPB is associated with a significant but brief reduction in postoperative production of cTnT. Subgroup analysis showed that dexamethasone does not improve postoperative production of cTnT either in cyanotic or in neonatal patients.

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