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ORIGINAL ARTICLE

A comparison of different management techniques for myocardial protection in acyanotic congenital cardiac patients

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Aim: It has already been shown that terminal warm blood cardioplegia (TWBC) supports myocardial protection in pediatric patients when it is administered after cold blood cardioplegia. However, the myocardial protective effects of TWBC applied after cold crystalloid cardioplegia (CCC) is still a subject of debate.

Materials and methods: Twenty acyanotic congenital cardiac patients were randomly divided into 2 groups of 10. In the control group (CG), moderate hypothermia, topical cooling, and cold crystalloid cardioplegia were performed for the protection of the myocardium. In the other group (TWBCG), the same procedure was supported using TWBC just before the unclamping of the aorta. Blood samples were analyzed to discover the progression of anaerobic energy metabolism potentially causing injury of the myocardium during the ischemic, reperfusion, and postoperative period.

Results: There were no significant statistical differences in age, body weight, mean pulmonary artery pressure, operation procedure, cardiopulmonary bypass and aortic cross clamping time, period of respiratory support, and intensive care unit and hospital stay. Also measurement of serum cardiac troponin T (TnT), creatine kinase MB(CK-MB), and lactate levels preoperatively, just after the release of the cross clamp and at the time of postoperative 4, 12, 24, and 48 h showed no significant differences either.

Conclusion: TWBC was not able to enhance the myocardial protective effects in acyanotic congenital cardiac patients when performed in addition to CCC.

Key words: Myocardial protection, terminal warm blood cardioplegia, cold crystalloid cardioplegia

Asiyanotik konjenital kalp hastalarında farklı myokard koruma tekniklerinin karşılaştırılması

Amaç: Sıcak kan kardiyoplejisinin soğuk kan kardioplejisini takiben uygulanmasının çocuk hastalarda myokardın korunmasını desteklediği zaten gösterilmiştir. Ancak sıcak kan kardiyoplejisinin soğuk kristaloid kardiyopleji sonrası kullanıldığındaki myokardiyal koruyucu etkisi hala tartışmalıdır.

Yöntem ve gereç: 20 asiyanotik konjenital kalp hastası her iki grupta da 10 hasta olacak şekilde rastgele olarak ikiye bölündü. Kontrol grubunda myokard koruması için orta hipotermi, topikal soğutma ve soğuk kristaloid kardiopleji uygulandı. Diğer grupta ise aynı prosedür kros klemp kalkmadan hemen önce terminal sıcak kan kardioplejisi verilerek desteklendi. Kan örnekleri iskemik, reperfüzyon ve post-operatif dönemde hasara neden olan anaerobik enerji metabolizmasının ilerleyişini tespit edebilmek için analiz edildi.

Bulgular: Yaş, ağırlık, ortalama pulmoner arter basıncı, operasyon prosedürü, kardiopulmoner bypass ve aortik kros klemp süresi, respirator destek süresi ile yoğun bakım ve hastanede kalış sürelerinde belirgin bir istatistiksel farklılık yoktu. Ayrıca Troponin T, Kreatinin Kinaz MB ve Laktat serum düzeylerinin preoperatif, kros klemp kaldırıldıktan hemen sonra ve post-operatif 4, 12, 24 ve 48. saatlerdeki ölçümlerinde de belirgin bir istatistiksel farklılık saptanmadı.

Sonuç: Terminal sıcak kan kardioplejisi, asiyanotik konjenital kalp hastalarında soğuk kristaloid kardiopleji ile birlikte kullanıldığında myokardiyal koruyucu etkileri arttırmakta yeterli olamamıştır.

Anahtar sözcükler: Myokardiyal koruma, terminal sıcak kan kardiopleji, soğuk kristaloid kardiopleji

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Introduction

To discover the most appropriate means of myocardial protection is one of the most desirable points of cardiac surgery, whether in adult or pediatric patients. To protect the myocardium from ischemia is as important as to be able to perform a successful surgical correction.

Inadequate myocardial protection procedures are responsible for most of the morbidity and mortality complications in congenital cardiac patients (1).

The reduction of the metabolic activity and the therapeutic arrest of the contractile apparatus are the main principles of myocardial protection (2). Hypothermia was regarded as an indispensable step for myocardial protection until the 1950s, after Bigelow pointed out the decrease in oxygen consumption in hypothermic conditions (3). Besides the metabolic reduction accomplished by hypothermia, myocardial protection must also be supported by the pharmacological arrest of the heart in diastole via cardioplegic solutions because of the necessity of minimizing energy production and to reduce the effects of ischemic damage on the myocardium.

The controversy about the most convenient choice of the cardioplegic solution in adults seems to be solved. Cold blood cardioplegia (CBC) applied after the clamping of the aorta (single shot) or administered repetitively (multi dose) and TWBC infused before unclamping of the aorta together is accepted to be the best choice for myocardial protection in adults with respect to the additional protective effects of TWBC to the CBC such as limitation in the reperfusion injury thereby improving the delivery of oxygen and stored cellular energy products to the arrested myocardium and vitally important washout of the anaerobic metabolic products to supply a better means to preserve phosphorilated energy products (1,4,5). However, because of the structural, functional, and biochemical differences between mature and immature myocardium, adult cardio-protective strategies should not be adopted in pediatric practice. In immature hearts, this cardioplegia technique has been shown to be of greater effect in myocardial protection by a few experimental animal studies (6-8) whereas it has only rarely been used in human pediatric patients (9,10).

The superiority of CBC+TWBC to the other types of cardioplegic procedures is proved to be especially for cyanotic pediatric patients because of their intolerance to ischemia. Although CBC, CBC+TWBC, and CBC+ TWBC+ substrate enhancement usage is gradually expanding among the pediatric cardiac surgeons all over the world, CCC is still the most commonly used procedure by pediatric cardiac surgeons because of its ease of use (11). In acyanotic pediatric patients, especially with short cross clamping time, the method of cardioplegia procedure appears not to be critical (9,12).

We use CCC to achieve the protection of myocardium for congenital cardiac patients in our clinic but planned to improve the myocardial protective effects of CCC by the addition of TWBC thereby reducing the detrimental effects of the reperfusion injury so that the aim of this study is to assess myocardial protective performance of CCC in combination with TWBC in acyanotic congenital cardiac patients.

Materials and methods

Twenty acyanotic congenital cardiac patients admitted to the Cardiovascular Surgery Department of Hacettepe University, Ankara, between December 2004 and April 2005 were selected for this study.

The study was approved by the Institutional Review Board of the Medical Faculty of the University. Patients were recruited to the study after the written informed consents were obtained from their parents.

They were randomly allocated into 2 groups of 10 patients, in order to observe differences in myocardial protection. Myocardial protection was performed by moderate hypothermia (20-28°C), topical cooling and antegrade CCC [(30 mL/kg, 4 °C) St Thomas I crystalloid cardioplegia; 20 mmol/L KCl, 16 mmol/L $MgCl_2$, 2.2 mmol/L $CaCl_2$, 144 mmol/L NaCl, and 1.0 mmol/L procaine HCl] applied after cross clamping of the aorta in the first group. In the second group, in addition to CCC, TWBC [(35 °C, 10 mL/kg) 4:1 dilution blood/St Thomas I crystalloid cardioplegia] was administered just before the unclamping of the aorta.

Patient mopulation

Preoperative patient characteristics with respect to age, body weight, sex, mean pulmonary artery pressure, and the pathologies of the patients were similar in the groups (Table 1).

Technique of cardiopulmonary bypass and myocardial protection

After heparinization (3 mg/kg) and controlling activated clotting time, CPB was initiated using ascending aorta and bicaval venous cannulation. Moderate hypothermia was performed in each group. In the CG (30 mL/kg, 4 °C) the cardioplegic solution was infused after the cross clamping of the aorta, in order to achieve the diastolic cardiac arrest. The solution was infused antegrade through an aortic root cannula, established while topical cooling by ice slush was performed in this group.

In the TWBCG, TWBC (10mL/kg, 35 °C) was infused in addition to CCC solution, just before the unclamping of the aorta. There was no topical cooling in this group.

In both groups, the aortic root pressure was measured during cardioplegic delivery and was held in the range of 40-60 mmHg. Defibrillation was performed when ventricular fibrillation occurred after the release of the cross clamp of the aorta. Weaning from CPB was accomplished if systolic blood pressure was not below 50-70 mmHg, urine output was adequate and nasopharyngeal temperature was 37 °C.

Anesthetic procedure

Patients were premedicated with a 0.1 cc/kg combination of Pethidine HCl, Pheniromine hydrogen maleate, and Chlorpromazine just an hour before the operation. Anesthesia was induced by Fentanyl Citrate and patients were mechanically ventilated after the administration of Cisatracurium besylate. Sefazolin and Gentamicin sulfate were given routinely. Anesthesia was perpetuated by Sevoflurane after cardiopulmonary bypass (CPB). As soon as the operation was ended, patients were transported to the intensive care unit (ICU) and weaned when all the extubation criteria were obtained.

Table 1. Patient characteristics.

	CG	TWBCG	P value
Age (month)			
mean	35.1 ± 26.04	54.7 ± 60.02	P > 0.05
range	7-96	4-168	
Sex (M/F)	6/4	4/6	
Weight (kg)	13.0 ± 5.8	14.0 ± 11.5	P > 0.05
mPAP	29.75 ± 13.96	35.3 ± 16.83	P > 0.05
Pathology			
ASD	4	3	
VSD	0	4	
VSD, PDA	1	1	
SM	0	1	
VSD, PFO	1	1	
VSD, SM	1	0	
ASD, PAPVD	1	0	
VSD, PDA, SM	1	0	
ASD, VSD, MR	1	0	

mPAP, mean pulmonary arterial pressure; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; SM, subaortic membrane; PFO, patent foramen ovale; PAPVD, partial anomalous pulmonary venous drainage; MR, mitral regurgitation.

Evaluation of the clinical results before and after the surgery

Clinical parameters included patients on whom right ventriculotomy was performed, the duration of CPB and aortic cross clamp, heart beat recovery after the release of the aortic cross clamp, either spontaneously or by electrical defibrillation and intraoperative requirement of (+) inotropes for weaning patients from CPB. Postoperative parameters included the initiation, duration, and the maximum doses of (+) inotrope dopamine, ventilation time, intensive care unit and hospital stay, also the mortality rate.

Measurements

Serum concentrations of TnT, CK-MB, and lactate were determined prior to the operation, just after the release of the aortic cross clamp, and 4, 12, 24, and 48 h postoperatively. Blood lactate concentrations were analyzed using P modular-p 800 (Roche Diagnostics, Indianapolis, Indiana, USA), whereas TnT and CK-MB assays were performed on an Elecsys-2010 platform (Roche Diagnostics).

Conventional thresholds for the diagnosis of TnT, CK-MB, and lactate levels are 0.0-0.1 ng/mL, 0.0-5.0 ng/mL, and 4.5-19.5 mg/dL, respectively.

Statistical analysis

Data are presented as mean values ± standard deviation. Testing of demographic variables was compared by unpaired t-test. Differences of variables between both groups were calculated with the Mann-Whitney U test. A P-value of <0.05 was chosen to define statistical significance. The statistical analysis was performed with the Stat View software package (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

Clinical outcome

There were no significant differences between the groups in the evaluation of the collected data. Right ventriculotomy was performed for one patient in each group when it was not possible to gain optimum sight of the ventricular septal defect (VSD) through the right atriotomy. Duration of CPB and aortic cross clamp were both longer in TWBCG than CG but no significant differences were observed. Electrical defibrillation when ventricular fibrillation occurred after the release of the cross clamp was necessary for 1 patient in TWBCG and 2 in the CG. It was not necessary to initiate (+) inotropes during the weaning period from CPB. The results are shown in Table 2. Ventilation time, intensive care unit, and hospital stay parameters showed no significant differences between the groups, and there were no mortalities in either group (Table 3).

Laboratory parameters

Troponin T

Increasing values of serum TnT were apparent until 4 h postoperatively. Parameters of serum TnT in

Table 2. Intraoperative variables.

	CG (n = 10)	TWBCG (n = 10)	P value
Right ventriculotomy	1	1	P > 0.05
CPB	54.7 ± 16,17	63.2 ± 24.7	P > 0.05
ACC	35.30 ± 14.25	44.5 ± 22.26	P > 0.05
Spontaneous heart beat recovery after ACC	8	9	P > 0.05
(+) inotropes during the weaning period from CPB	0	0	

Data are presented as mean values ± standard deviation. A P value of <0.05 was chosen to define statistical significance. CPB, cardiopulmonary bypass; ACC, aortic cross clamp

Table 3. Postoperative findings.

	CG (n = 10)	TWBCG (n = 10)	P value
Duration of (+) inotropes (hour)	130	93	P > 0.05
Ventilation support (hour)	8.30 ± 4.40	9.00 ± 6.18	P > 0.05
ICU stay (day)	2.6 ± 0.7	2.9 ± 1.2	P > 0.05
Hospital stay (day)	8.2 ± 5.92	6.9 ± 1.37	P > 0.05

Data are presented as mean values ± standard deviation. A P value of < 0.05 was chosen to define statistical significance. ICU, intensive care unit.

the CG displayed an increasing rate higher than the TWBCG. Serum TnT values began to decrease after 4 h to 24 h postoperatively, in both groups. A slight raise existed in CG whereas the decreasing period went on in TWBCG, but there were no significant differences (Figure 1).

CK-MB

CK-MB serum levels were higher in the CG than the TWBCG after release of the cross clamp. CK-MB levels continued to increase to 4 h postoperatively in both groups, minimally more in TWBCG than CG. The downward slope of CK-MB levels initiated after 4 h and went on till 48 h postoperatively (Figure 2).

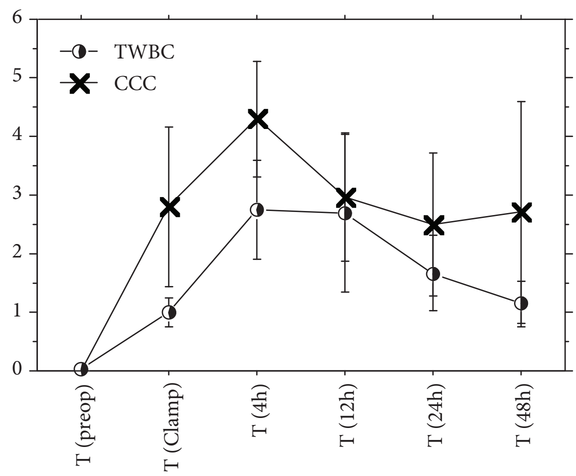

Figure 1. Serum cardiac TnT levels. Data are presented as mean values ± standard deviation. A P value of <0.05 was chosen to define statistical significance. Troponin T (ng/mL).

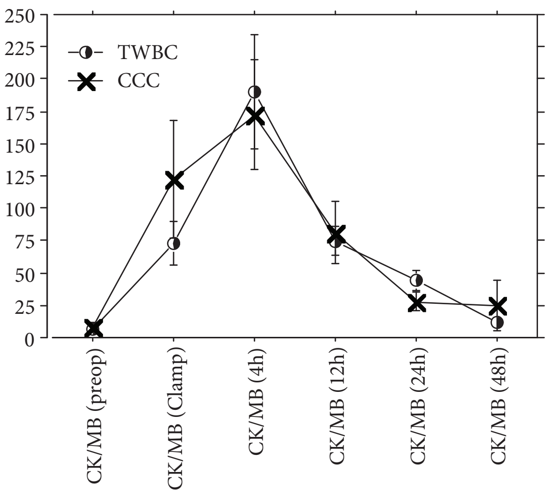

Figure 2. Serum concentration of CK-MB levels. All results are shown as mean values ± standard deviation. A P value of <0.05 was chosen to define statistical significance. CK-MB (ng/mL).

Lactate

The results of serum lactate levels at the time of unclamping of the aorta were high in both groups, being slightly higher in the TWBCG. After 4 h, lactate levels of CG showed a curve higher than TWBCG, especially between 24 and 48 h but demonstrated no significant differences (Figure 3).

Discussion

Post-ischemic reperfusion-induced injury is a paradoxical extension of ischemic damage that occurs during reperfusion after myocardial ischemia (13). If a reperfusion injury occurs, it may contribute to troublesome arrhythmias, impaired cardiac

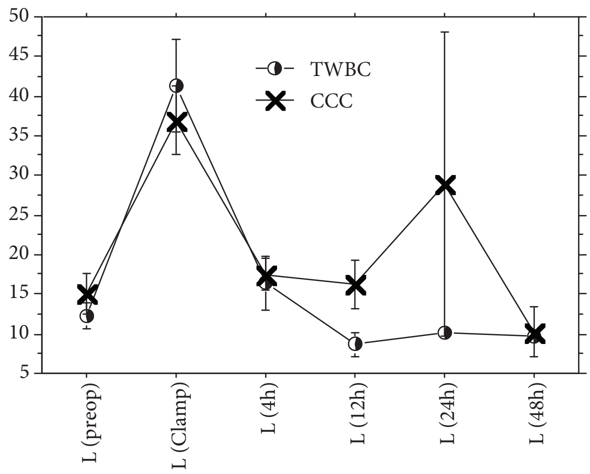

Figure 3. Serum concentration of lactate levels. Data are presented as mean values ± standard deviation. A P value of <0.05 was chosen to define statistical significance. Lactate (mg/dL).

performance developing immediately after the operation, and to the eventual myocardial fibrosis that may result after even a perfect surgical correction of congenital or acquired cardiac diseases (14,15). This potential for reperfusion injury may exist after all of the cardiac operations where coronary circulation is interrupted by cross clamping of the aorta. To deal with reperfusion injury is considered to be the main object of a myocardial protective procedure, especially in infants undergoing corrective surgery (16).

TWBC has begun to be used to reduce the detrimental effects of reperfusion injury. It is specifically formulated for this purpose and its composition is vastly different from the cardioplegic solution used for maintaining myocardial arrest (1,17).

The advantages of TWBC applied after a single shot or multi-dose repetitive cold blood cardioplegia are demonstrated in recent studies with encouraging clinical results, showing that this myocardial protective procedure is expanding all over the world (6,7,9,10).

Even though CCC is still the most common procedure for myocardial protective techniques in congenital cardiac surgery, there is no study in the literature that evaluates its performance in combination with TWBC.

Our results showed no significant differences between the 2 described myocardial protection methods. Although we expected the results to be better in the TWBC group, this was not the case. However, serum TnT and CK-MB levels, which may indicate a marker for myocardial injury, showed a lower curve tendency in the TWBC than in the CG, although not in a significant way. Increasing values of serum lactate is one of the most significant predictors of dangerous levels of the anaerobic metabolism, acidosis, and the threat of dysfunction to the heart. However, the lactate levels are not specific markers for heart damage if they are taken systemically rather than directly from the coronary sinus. This is one of the main limitations of our study. The small number of patients in this study is also an important drawback for the statistical analysis of the results. Although we were unable to demonstrate the advantages of TWBC in this randomized study, more extensive research in this area is needed with a greater number of patients. Since this study is limited to acyanotic infants who may have decreased ischemic cardiac injuries compared to cyanotic and older patients with a variety of cardiac diseases, the findings are not clear enough to suggest any changes in the protective myocardial management techniques.

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