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Comparison of Custodiol® and modified St.Thomas cardioplegia for myocardial protection in coronary artery bypass grafting

Poređenje Custodiol®-a i modifikovane St. Thomas kardioplegije u zaštiti miokarda tokom operacije aortokoronarnog premošćavanja

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Abstract

Background/Aim. Custodiol® is a hyperpolarizing cardioplegic solution which has been used in our national cardiac surgical practice exclusively for the heart transplant surgery. Owing to its numerous advantages over the standard depolarizing solutions, Custodiol® became cardioplegic solution of choice for all other cardiac surgical procedures in many cardio-surgical centers. This study evaluated myocardial protection by Custodiol® compared to modified St. Thomas cardioplegic solution in coronary artery bypass surgery. **Methods.** In a prospective four-month study, 110 consecutive adult patients who underwent primary isolated elective on-pump coronary artery bypass grafting (CABG) were randomized into the Custodiol® group (n = 54) and the St. Thomas groupa (n = 50), based on the type of administered cardioplegia; six patients were excluded. Cardiac protection was achieved as antegrade cold crystalloid cardioplegia by one of the solutions. Myocardial preservation was assessed through following outcomes: spontaneous rhythm restoration post cross-clamp, and postpoperative cardiac specific enzymes level, ejection fraction (EF) change, inotropic support, myocardial infarction (MI), atrial fibrillation (AF), and death. **Results.** Preoperative and intraoperative characteristics of patients in both groups were similar except for a considerably longer cross-clamp time in the Custodiol® group (49.1 ± 19.0 vs. 41.0 ± 12.9 minutes; $p = 0.022$). The Custodiol® group exhibited a higher rate of return to spontaneous rhythm compared to the St. Thomas group (31.5% vs. 20.0%, respectively; $p = 0.267$), lower rates of AF (20.4% vs. 28%, respectively; $p = 0.496$), MI (1.8% vs. 10.0%, respectively; $p = 0.075$) and inotropic support (9.0% vs. 12.0%, respectively; $p = 0.651$), albeit not statistically significant. There was an insignificant difference in peak value of troponin I between the Custodiol® and Thee St. Thomas group (5.0 ± 3.92 μg/L vs. 4.5 ± 3.39 μg/L, respectively; $p = 0.755$) and creatine kinase-MB (26.9 ± 15.4 μg/L vs. 28.5 ± 24.2 μg/L, respectively; $p = 0.646$) 6 hours post-surgery. EF reduction was comparable (0.81% vs. 1.26%; $p = 0.891$). There were no deaths in both groups. **Conclusions.** Custodiol® and modified St.Thomas cardioplegic solution have comparable cardioprotective effects in CABG surgery. The trends of less frequent MI, AF and inotropic support, despite the longer cross-clamp time in the Custodiol® group may suggest that its benefits could be ascertained in a larger study.

Key words:
heart arrest, induced; custodiol-n solution; cardiac surgical procedures; postoperative period; arrhythmias, cardiac; heart function tests; mortality.

Apstrakt

Uvod/Cilj. Custodiol® je hiperpolarizirajući kardioplegični rastvor koji je korišćen u našoj nacionalnoj kardiohirurškoj praksi isključivo u transplantacionoj hirurgiji. Zbog svojih brojnih prednosti u odnosu na standardne depolarizirajuće rastvore, Custodiol® je, u mnogim kardiohirurškim centrima, postao kardioplegični rastvor izbora za sve kardiohirurške procedure. Cilj studije bio je procena zaštite miokarda rastvorom Custodiol® u poređenju sa modifikovanom St. Thomas kardioplegičinim rastvorom u koronarnoj hirurgiji. **Metode.** Tokom prospektivne četveromesečne studije, 110 uzastopnih odraslih bolesnika podvrgnutih primarnoj, izolovanoj, elektivnoj operaciji aortokoronarnog premošćavanja bili su randomizirani na osnovu primenjene kardioplegije u Custodiol® grupu (n = 54) i St. Thomas grupu

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(n = 50); šest bolesnika je bilo isključeno iz studije. Zaštita miokarda izvršena je primenom antegradne, hladne kristaloidne kardioplegije jednim od rastvora, a procenjena je praćenjem sledećih parametara: spontane uspostave srčanog ritma nakon deklemovanja; vrednosti kardiospecifičnih enzima; promene ejekcione frakcije (EF) 24 sata nakon operacije; učestalosti postoperativne inotropne potpore, infarkta miokarda (MI), atrijalne fibrilacije (AF) i smrti. **Rezultati.** Preoperativne i intraoperativne karakteristike bolesnika bile su slične u obe grupe, osim značajno dužeg vremena klemovanja u Custodiol® grupi (49,1 ± 19,0 min. vs. 41,0 ± 12,9 min; $p = 0,022$). Custodiol® grupa, u odnosu na St. Thomas grupu, imala je češću spontanu uspostavu srčanog ritma (31,5% vs. 20,0%, $p = 0,267$), uz nižu učestalost AF (20,4% vs. 28%, $p = 0,496$), MI (1,8% vs. 10,0%, $p = 0,075$) i inotropne podrške (9,0% vs. 12,0%, $p = 0,651$), ali bez statističke značajnosti. Maksimalne vrednosti troponina I (5,0 ± 3,92 μg/L vs. 4,5 ± 3,39 μg/L; $p = 0,755$) i kreatin kinaze-MB (26,9 ± 15,4 μg/L vs. 28,5 ± 24,2 μg/L; $p = 0,646$) bile su slične, šest sati nakon operacije. U obe došlo je do je sličnog smanjenja EF (0,81% vs. 1,26%; $p = 0,891$) bez mortaliteta unutar 30 dana nakon operacije. **Zaključak.** Custodiol ima sličan kardioprotektivni efekat u poređenju sa modifikovanim St. Thomas kardioplegičnim rastvorom kod operacije aortokoronarnog premošćavanja. Zbog dužeg vremena klemovanja aorte, uz istovremeni trend manje učestalosti MI, AF i inotropne podrške u grupi sa rastvorom Custadiol®, studija na većem broju bolesnika mogla bi otkriti prednosti Custadiol®-a u zaštiti miokarda tokom operacije aortokoronarnog premošćavanja.

Ključne reči:
srce, izazvani zastoj; custodiol-n rastvor; hirurgija, kardijalna, procedure; postoperativni priod; aritmija; srce, funkcijski testovi; mortalitet.

Introduction

Cardiac surgery is always accompanied by a certain degree of myocardial damage which is multifactorial and cumulative, but ischemia-reperfusion injury is the major factor inducing intraoperative myocardial damage [1]. Myocardial protective strategies during cardiac surgery aim to diminish ischemia-reperfusion myocardial injury that could cause myocardial infarction (MI), arrhythmias, ventricular dysfunction and low cardiac output syndrome (LCOS). Atrial fibrillation (AF), the need for inotropic support, acute renal injury, prolonged intensive care unit (ICU) stay, and death are the most common consequences of LCOS [1, 2]. There are numerous methods of myocardial protection during cardiac surgery, but cardiopulmonary bypass (CPB), hypothermia, and cardioplegic arrest remain the primary protective techniques during open heart surgery [2–4]. Cardioplegia, as a method of myocardial protection, has been in use for almost half a century. Crystalloid cardioplegic solutions could be categorized according to the electrolyte composition into two types: extracellular and intracellular type. Extracellular solutions contain higher concentration of sodium, calcium, and magnesium and produce depolarizing cardiac arrest. Intracellular solutions with a low concentration of sodium and calcium, induce cardiac arrest by hyperpolarization. St.Thomas Hospital solution and its modifications are the best known and longest used extracellular crystalloid cardioplegia [2]. Bretschneider histidine-tryptophan-ketoglutarate solution, known as Custodiol® (Custodiol® HTK, Köhler Chemie GmbH, Bensheim, Germany), is an example of an intracellular crystalloid cardioplegic solution [4]. Custodiol® is an intracellular, hyperpolarized, crystalloid solution commonly used for organ preservation in heart transplant procedure, but its use for myocardial protection in ordinary cardiac surgery has not been established entirely and remains an off-label indication in many countries. Custodiol® solution administered in a single dose provides up to 2–3 hours of myocardial protection, which is an advantage over alternative cardioplegic solutions requiring re-administration every 20–30 min. Moreover, cardiac arrest induced by hyperpolarization mimics natural resting state of the heart and minimize metabolic demand decreasing adenosine triphosphate (ATP) depletion thus improving the conditions of the heart to be reanimated at the end of the procedure.

Custodiol® contains a low sodium concentration that causes hyperpolarization and prevents edema and a high concentration of histidine with high buffering capacity, effective under hypothermic conditions, which may enhance the efficiency of anaerobic glycolysis. Furthermore, Custodiol® contains mannitol, ketoglutarate and tryptophan. Mannitol and histidine as well are free radical scavengers that decrease cellular edema. Ketoglutarate is an intermediate in the Krebs cycle and increases energy production upon reperfusion, whereas tryptophan stabilizes cell membranes [4, 5].

Custodiol® has been used in our national cardiac surgical practice exclusively as an organ preserving solution for the heart transplant surgery, with a special supply permission, since it is not yet registered at the Medicines and Medical Devices Agency of Serbia (MMDS). Standard strategy, with modified extracellular St.Thomas cardioplegic solution has been used for decades in adult cardiac surgical patients, and thus, it is registered at the MMDS. Due to its numerous advantages over the standard, depolarizing solutions, Custodiol® became the first choice solution for all other, non-transplant cardiac surgical procedures, in the most cardiac surgical centers worldwide. Our intention to start a new strategy, with routine use of intracellular Custodiol® solution for non-transplant cardiac surgical patients, came from well known advantages of this solution.

There is still no clear evidence nor consensus among cardiac surgeons and anesthesiologists as to which cardioplegia provides the best myocardial protection. The ideal composition and method of using cardioplegic solution are still open questions [4]. The aim of this study was to evaluate myocardial protection of Custodiol® compared to modified St. Thomas cardioplegia in adult coronary artery bypass surgery.

Methods

Patient population

The prospective randomized study included 110 consecutive adult cardiac patients (pts), between February and June 2018, who underwent primary isolated and elective coronary artery bypass grafting surgery (CABG), in condition of extracorporeal circulation.

The study protocol followed the Declaration of Helsinki and was approved by the Institution's Ethics Committee. Informed consent was obtained from each patient.

Inclusion criteria were**:** adult elective coronary patients with minimun two angiographic graftable target vessels (diameter > 2.0 mm with stenosis ≥ 70%), LVEF (left ventricular ejection fraction) ≥ 30%, ultrasonography verified absence of significant valvular pathology.

Exclusion criteria were older than 80 years, myocardial infarction within 30 days of the operation, reoperations, urgent/emergent patients, off-pump CABG, left main stenosis > 50%, ongoing myocardial ischemia [verified by electrocardiogram (ECG) and elevated cardiac troponin I (cTnI) and/or creatine kinase MB (CK-MB) isoenzyme], pericarditis, serum creatinine level > 200 μmol/L, coronary artery endarterectomy, and left ventricular surgical restoration.

Patients who met the inclusion criteria of the study were randomized into two groups: the group receiving standard modified St.Thomas cardioplegic solution (St. Thomas M) according to the Hospital protocol, and the group receiving one bolus (20 mL/kg) of Custodiol® HTK Solution, during six to eight minutes (Table 1).

Six patients were subsequently excluded from the study after randomization due to: myocardial infarction during anesthesia induction – 1 patient, errors in the cardioplegia delivery protocol – 3 patients, endarterectomy of coronary artery – 1 patient, and left ventricular restoration surgery – 1 patient.

Anesthesia and operative technique

Anesthetic induction was performed with midazolam (0.1 mg/kg), hypnomidate (0.2 mg/kg), rocuronium bromide (0.6 mg/kg) and sufentanil (1 μg/kg). Maintenance of anesthesia was provided by sufentanil (0.02–0.05 μg/kg/min), sevoflurane (0.8–1.5 vol%) and rocuronium bromide (8–10 μg/kg/min). Standard operative technique through total median sternotomy was used for all patients. Cardiopulmonary bypass in condition of mild systemic hypothermia (32 °C to 34 °C) was established with ascending aortic cannulation and right atrial two-stage venous cannulation after systemic heparinization (4 mg/kg) with a target activated clotting time greater than 480 s. Standard management included membrane oxygenators, roller pump with a non-pulsatile flow of 2–2.4 L/min/m^2 with a mean arterial blood pressure around 60 mmHg. After CPB was discontinued, heparin was neutralized with 0.8 mg protamine sulfate *per* 1 mg of heparin. Cell saver and tranexamic acid (30 mg/kg) were routinely used. Myocardial protection was achieved by one of the two study solution as antegrade intermittent cold crystalloid cardioplegia (4–8ºC) and topical cooling with iced saline "slush". Cardioplegic solutions were administrated as follows: St.Thomas M induction dose was 1,000 mL over 3–5 min with maintenance doses of 200 mL over 2 min every 20 min thereafter; Custodiol® was delivered as one single dose of 20 mL/kg over 6–8 min whereas the second dose was provided only when the cross-clamp time exceeded 120 min. If the heart exhibited electrical or mechanical activity during the procedure, additional doses of 200 mL of the cardioplegic solution was administered. The composition of modified St Thomas [5] cardioplegic solution routinely used in our Institution was: Na^+ 147 mM/L, K^+ 20 mM/L, Mg^{2+} 16 mM/L, Ca^{2+} 2 mM/L, Cl^- 203 mM/L, $NHCO3^-$ 10 mM/L, Osmolality 388 mOsm/kg, pH(25°C) ~ 7.8, and the composition of the Custodiol® [7] was: Na^+ 15 mM/L, K^+ 9 mM/L, Mg^{2+} 4 mM/L,Ca^{2+} 0.015 mM/L, histidine 198 mM/L, Tryptophan 2 mM/L, ketoglutarate 1 mM/L, mannitol 30 mM/L, osmolality 310 mOsm/kg, pH(25°C) ~ 7.02–7.20.

Perioperative transfusion, fluid administration, and use of inotropes and vazopressor were carried out at the discretion of anesthesiologists.

As primary outcome measures we compared: cTnI levels preoperative, 6, 24 and 48 hours post surgery, and changes in LVEF by transthoracic echocardiogram (TTE), 24 hours post surgery.

As a secondary outcome measures, we compared: 30-day mortality; CK-MB levels preoperative, 6, 24 and 48 hours post surgery; time to cardiac arrest (time elapsed from the introduction of cardioplegic infusion to the cessation of cardiac electrical and mechanical activity); spontaneous rhythm restoration post aortic cross-clamp (ACC); prolonged mechanically assisted ventilation (MV) ≥ 24 h, up to 48 hours post surgery; inotropic support ≥ 60 min, up to 48 hours post surgery; MI, up to 48 hours post surgery; AF *de novo*, up to 48 hours post surgery; prolonged ICU and hospital length of stay (LOS) > 3 days; other postoperative morbidity [infection (deep wound infection or sepsis), stroke, acute kidney injury].

Data collection and definitions

Twelve-lead ECG was routinely obtained preoperatively at the ICU at arrival and daily until ICU discharge, and whenever the clinical situation of the patient required it. All ECGs were compared with the preoperative recording for evidence of new postoperative infarction. Heart rhythm and rate were monitored continuously with telemetry during the ICU stay. Patients who suffered at least one episode of AF postoperatively, without history of AF preoperatively, and needed medical treatment were recorded.

TTE examinations were performed preoperatively and about 24 hours post-surgery by two highly experienced echocardiographers. Left ventricular (LV) ejection fraction was estimated by biplane Simpson's method. Regional wall motion abnormalities were visually assessed and were

marked as akinetic, dyskinetic, or hypokinetic segments. Occurrence of new postoperative segmental wall motion defects or deterioration of the existing one, compared with the preoperative echocardiography, were registered. Left ventricle walls thickness more than 11 mm was considered as a marker of left ventricular hypertrophy.

Cardiac markers (cTnI, CK-MB) were determined in peripheral blood preoperatively (T0), at 6 (T6), 24 (T24) and 48 (T4) hours postoperatively according to profile of enzymes release after on-pump CABG [7]. cTnI and CK-MB were measured quantitatively by means of enzyme electrochemiluminescence immunoassay (Beckman Coulter Access 2 Analyzer): the upper normal reference limit (URL, 99th percentile) for cTnI was 0.05 μg/L and for CK-MB these values were 7.2 μg/L for male and 3.4 μg/L female.

Criteria for MI were: peak of cTnI value > 3.1 μg/L within 48 hours after operation, with normal preoperative values, associated with either ECG showing new pathological Q waves or new left bundle branch block (LBBB) or TTE revealing new regional hypokinetic or akinetic area in the left or right ventricle [6, 8].

Acute kidney injury (AKI) was defined as an increase in serum creatinine to ≥ 2 times baseline

Statistical analysis was performed using the IBM SPSS statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ±standard deviation or median and interquartile range, whilst categorical variables were given as absolute values and percentages.

Table 1

Baseline characteristics and patient comorbidities

Parameters	Custodiol® group (n = 54)	St Thomas M group (n = 50)	*p value*
Age (years)	64.5 ± 6.5(65.0; 61.8–69.0)	65.3 ± 6.3(65.00; 61.8–70.0)	0.546[a]
Male sex	40 (74.1)	44 (88.0)	0.121[b]
BMI (kg/m^2)	1.95 ± 0.18(1.94;1.87-2.02)	1.96 ± 0.14(1.96;1.85-2.04)	0.970[a]
Risk factors			
Hypertension	40 (74.1)	44 (88.0)	0.121[b]
Diabetes mellitus/insulin-treated	24 (44.4)/4 (7.4)	20(40.0)/11(22.0)	0.795/0.066[b]
Dyslipidemia	24 (44.4)	24 (48.0)	0.868[b]
Active smoker	21 (38.9)	21 (42.0)	0.902[b]
Comorbidity non cardiac			
CKD:GFR < 60 mL/min/1.73 m^2	8 (14.8)	9 (18.0)	0.862[b]
COPD	3 (5.6)	5 (10.0)	0.630[b]
Carotid disease	5 (9.3)	5 (10.0)	1.000[b]
PVD	5 (9.3)	4 (8.0)	1.000[b]
Comorbidity cardiac			
Previous LVEF	57.9 ± 7.9 (58.0;52.0–64.0)	55.2 ± 8.1(56.0; 48.8–62.5)	0.116[a]
LV hypertrophy	10(18.5)	3 (6.0)	0.103[b]
Atrial fibrillation	11(20.4)	6 (12.0)	0.375[b]
NYHA class	1.57 ± 0.60 (2;1–2)	1.6 ± 0.62 (2;1–2)	0.673[c]
CCS	2.09 ± 0.87 (2;2–2)	1.86 ± 0.88 (2;1–2)	0.363[c]
Prior MI *per* patient	0.76 ± 0.08 (1;0–1)	0.82 ± 0.66 (1;0–1)	0.709[c]
Prior MI n (%) of patients	38 (70.4)	34 (68.0)	0.289[b]
STEMI/NSTEMI	18 (42.9)/24 (57.1)	22 (53.7)/19 (46.3)	0.302/0.348[b]
Prior PCI	14 (26.4)	12 (24.0)	0.956[b]
Diseased vessels	3.37 ± 0.83 (3; 3–4)	3.14 ± 0.83 (3; 3–4)	0.192[c]
Syntax score	29.8 ± 9.4 (29.0; 22.0–36.5)	29.1 ± 8.8 (28.0; 21.9–35.5)	0.713[c]
EuroScore II	1.15 ± 0.73 (0.92; 0.64–1.59)	1.14 ± 0.48 (1.10 ; 0.71–1.54)	0.452[a]
Preoperative drug therapy			
β-blockers	46 (85.2)	44 (88.0)	0.894[b]
Loop diuretics	10 (18.5)	7 (14.0)	0.721[b]
Acetylsalicylic acid	54 (100.0)	49 (98.0)	0.969[b]
trimetizidine	5 (9.3)	15 (30.0)	0.015[b]
Statins	42 (77.8)	44 (88.0)	0.264[b]
ACEI/ARB	51 (94.4)	46 (92.0)	0.916[b]

***Note*: Results are given as mean ± standard deviation (median; interquartile range) or number (percentage). BMI – body mass index; COPD – chronic obstructive pulmonary disease; PVD – peripheral vascular disease; MI – myocardial infarction; STEMI/NSTEMI – ST/non-ST segment elevation MI; PCI – percutaneous coronary intervention; PVD –peripheral vascular disease;LV – left ventricular;LVEF – LV ejection fraction (Simpson's method);CKD –chronic kidney diseases; GFR – glomerular filtration rate; CCS – Canadian Cardiovascular Society grading of angina pectoris;NYHA – New York Heart Association; Diseassed vessels – coronary stenosis > 70%; Syntax score – angiographic score of coronary artery disease complexity; Euro score – European System for Cardiac Operative Risk Evaluation; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker.**

[a]*t* test; [b]χ^2 test; [c]Mann-Whitney U test.

Table 2

Operative data and postoperative outcomes

Parameters	Custodiol® group (n = 54)	St Thomas M group (n = 50)	*p value*
CPB time (min)	82.2±23.7 (80.0; 63.3–94.0)	74.5 ± 18.5 (70.5; 60.0–84.0)	0.075[c]
ACC time (min)	49.1 ± 19.0 (45.5; 35.8– 60.2)	41.0 ± 12.9 (39.0; 30.0–50.2)	0.022[c]
Number of grafts	2.9 ± 0.9 (3;2–4)	2.7 ± 0.8 (3; 2–3)	0.593[c]
LITA	52 (96.3)	49 (98.0)	1.000[b]
T (sec)	59.3 ± 21.3	59.7 ± 30.0	0.388[c]
Amount of cardioplegia (mL)	1667 ± 268 (1600;1500 –1812)	1306 ± 251 (1300;1100–1350)	0.000[c]
Spontaneous rhytam after ACC	17 (31.5)	10 (20.0)	0.267[b]
Clinical outcomes			
LVEF postoperative	57.0 ± 8.5 (56.5; 50.0–65.0)	54.0 ± 8.0(55.0; 50.0–59.3)	0.073[a]
ΔEF	-0.8 ± 4.3(1.0; -2.0–4.0)	-1.16 ± 5.10(0.0;-2.3-5.0)	0,896[a]
Postoperative MI	1(1.8)	5(10.0)	0.075[b]
Atrial fibrillation *de novo*	11 (20.4)	14 (28.0)	0.496[b]
Inotropic support	5 (9.3)	6 (12.0)	0.893[b]
Reoperation for bleeding	2 (3.7)	4 (8.0)	0.604[b]
Drainage (mL)	745 ± 470 (635; 230–2400)	848 ± 414 (710; 444–1078)	0.292[c]
Transfusion (mL)	248 ± 345 (238; 0–303)	343 ± 414 (255; 0–559)	0.260[c]
Acute kidney injury	0 (0)	0 (0)	/
Stroke	0 (0)	0 (0)	/
Infection	1 (1.9)	1 (2.0)	1.000[b]
Prolonged MV > 24 h	0 (0)	0 (0)	/
ICU length of stay (days)	2.8 ±1.8 (2.0; 2.0–3.0)	3.4 ± 4.3 (2.0; 2.0–3.0)	0.395[c]
Prolonged ICU-LOS > 3 days	8 (14.8)	12 (24.0)	0.348[b]
Hospital (H) LOS (days)	7.7 ± 3.9 (7.0; 6.0–8.0)	8.0 ± 4.5 (7.0; 6.0–7.0)	0.811[c]
Prolonged H-LOS > 10 days	4 (7.4)	6 (12.0)	0.645[b]
30-day mortality	0 (0)	0 (0.0)	/

***Note*: Results are given as mean ± standard deviation (median; interquartile range) or number (percentage).**

CBP – cardiopulmonary bypass; ACC – aortic cross-clamp; LITA – left internal thoracic artery; T – time to cardiac arrest after ACC; LVEF – left ventricular ejection fraction; ΔEF = LVEF preoperative-LVEF 24 h- postoperative; MI – myocardial infarction; Drainage/Transfusion (mL) 48 hours post surgery; ICU – intensive care unit; LOS – length of stay; MV – mechanical ventilation; Infection – deep sternal wound infection or sepsis.

[a]*t* test; [b]χ^2 test; [c]Mann-Whitney U test.

A comparison of the two groups, i.e. two clinical treatments, was done using *t*-test and Mann-Whitney U-test for continuous variables and χ^2 test for categorical variables. *P* values < 0.0^5 were considered statistically significant.

Results

The study enrolled 104 patients of which 54 patients used Custodiol® and 50 patients used St. Thomas M cardioplegia for myocardial protection. Patients in both groups were well balanced with regard to the preoperative demographic and clinical characteristics (Table 1). Demographics data were similar, two-thirds of them were male, with a mean patient age about 65 years. There were no statistically significant differences between the subjects in any of the following variables displayed in Table 1: risk factors, non-cardiac and cardiac comorbidities. In terms of ischemic heart diseases, majority of patients had a three vessel coronary artery disease with medium to high degree of coronary disease extensity with regard to average value of SYNTAX score of 29. Furthermore, about half of patients suffered from moderate anginal disorders, class 2 according to the Canadian Cardiovascular Society (CCS) Angina Grading Scale. Most of the patients had previously survived one MI with preserved LV function and LVEF greater than 55%. They were categorized to the 2nd stage of heart failure according to the New York Heart Association (NYHA) classification. Left ventricular hypertrophy was three times more common in the Custodiol® group than in the St. Thomas M group (18.5% vs. 6.0%, respectively), but this difference did not reach statistical significance ($p = 0.103$). We noted that hypertrophied myocardium was more vulnerable to ischemic damage [1, 6]. Patients in both groups were consider to be at low surgical risk on the basis of log Euro Score II (European System for Cardiac Operative Risk Evaluation) with mean value of around 1. Considering preoperative therapy, patients in the St. Thomas M group notably more often used trimetizidine (a cardioprotective agent that reduce ischemia-reperfusion injury of the heart) compared with patients in the Custodiol® group, 30.0% vs. 9.3%, respectively ($p = 0.015$).

Table 2 presents the operative data and postoperative outcomes across the two groups. With regarding to the operative data, the average cardiopulmonary bypass time was

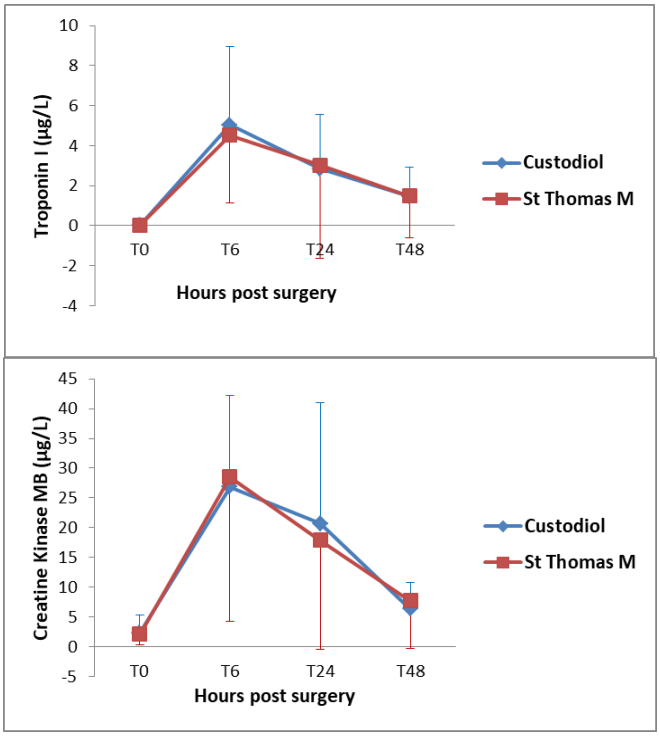

Fig. 1 – Enzyme level values over 48 hours post surgery (mean ± standard deviation).

Table 3

Cardiac enzymes at 6 and 24 hours post-surgery

Cardioplegic solution	cTnI (µg/L) peak level	CK-MB (µg/L) 6 horus post-surgery	cTnI (µg/L) prognostic level	CK-MB (µg/L) 24 hours post-surgery
Custodiol®	5.04 ± 3.92 (4.02;1.98–7.18)	26.89 ± 15.4 (25.10;14.40–37.35)	2.84 ± 2.74 (1.91; 0.91–4.13)	20.73 ± 20.20 (16.80; 8.62–23.75)
St.Thomas M	4.53 ± 3.39 (3.57;2.21–5.71)	28.50 ± 24.20 (21.30;14.42–35.38)	3.13 ± 4.68 (1.77;0.88–3.09)	18.10 ± 18.30 (12.00; 7,78–21,48)
*p**	0.755	0.646	0.571	0.164

***Note:* Results are given as mean ± standard deviation (median; interquartile range).**
cTnI – cardiac troponin I; CK-MB – creatine kinase-MB.
***Mann-Whitney U test.**

longer for the Custodiol® group compared to the St. Thomas M cardioplegia group, 82.2 ± 23.7 vs. 74.5 ± 18.5 min, respectively. This difference trended toward statistical significance with a *p* value of 0.075. The cross-clamp time difference between the groups reached statistical significance with a *p* value of 0.022 and were considerably longer for patients in the Custodiol® group (49.1 ± 19.0 min) compared to that in the the St. Thomas M group (41.0 ± 12.9 min). On the other hand, the number of grafts was similar, about 3 grafts *per* patient, and the internal mammary artery was used in over 95% of cases in both groups. Intraoperative parameters of cardioplegic efficiency, time to cardiac arrest, and spontaneous rhythm recovery rate were similar in both groups. The total amount of used cardiplegic solution was significantly higher in the Custodiol® vs. St.Thomas M group, 1,667 vs. 1,306 mL, respectively ($p = 0.000$). Postoperative complications data presented in Table 2 were comparable between the groups. With regard to postoperative clinical indicators of myocardial protection efficacy, the results were as follows: there were neither 30-day deaths nor prolonged MV over 24 hours in either group, the Custodiol® group showed less frequently AF (20.4% vs. 28.0%; $p = 0.496$), MI (1.8% vs. 10.0%; $p = 0.075$) and inotropic support (9.0% vs. 12.0%; $p = 0.651$) than the St.Thomas M group, but without statistical significance, LVEF reduction was comparable (0.81% vs. 1.26%; $p = 0.891$), prolonged ICU and hospital LOS were less frequent in the Custodiol® than in the St.Thomas M group, but with no statistical significance, (14.8% vs. 24.0%, $p = 0.348$ and 7.4% vs. 12.0% , $p = 0.645$, respectively).

In terms of cardiac enzymes, as markers of myocardial necrosis, no statistically significant difference was found in any of the sampling times as shown in Figure 1 and Table 3. The peak of the values of all enzymes was 6 after the surgery.

Composite indicator, myocardial protection efficacy (PMPE) was introduced to capture occurrence of infrequent clinically important outcomes. In particular, PMPE was defined as occurrence of one of following: postoperative MI, AF *de novo*, inotropic support, prolonged IUC lenght (ICU-LOS) > 3days, prolonged hospital LOS > 10 days, prolonged MV > 24 h, 30-day mortality, cTnI > 8.5 µg/L at 24 h post-

Table 4

Summarized factors of perioperative myocardial injury

Variable	Custodiol group (n = 54)	St Thomas M group (n = 50)	*p*
Predictors of perioperative myocardial injury and postoperative cardiac troponin I (cTnI) elevation [6, 7]			
Age (years)	64.5 ± 6.5 (65.0;61.8- 0)	65.3 ± 6.3 (65.00; 61.8-70.0)	0.546[a]
Female sex	14 (25.9)	6 (12.0)	0.121[b]
Previous LVEF	57.9 ± 7.9 (58.0; 52.0–64.0)	55.2 ± 8.1 (56.0; 48.8–62.5)	0.100[a]
LV hypertrophy	10 (18.5)	3 (6.0)	0.103[b]
Diseassed vessels	3.37 ± 0.83 (3; 3–4)	3.14 ± 0.83 (3; 3–4)	0.192[c]
CKD:GFR < 60mL/min/1.73m^2	8 (14.8)	9 (18.0)	0.862[b]
Preductal	5 (9.3)	15 (30.0)	0.015[b]
EuroScore II	1.15 ± 0.73(0.92; 0.64-1.59)	1.14 ± 0.48 (1.10 ; 0.71-1.54)	0.452[a]
CPB time	82.2 ± 23.7 (80.0; 63.3–94.0)	74.5 ± 18.5 (70.5; 60.0–84.0)	0.075[a]
ACC time (min)	49.1 ± 19.0 (45.5; 35.8– 60.2)	41.0 ± 12.9 (39.0; 30.0–50.2)	0.022[a]
Number of grafts	2.9 ± 0.9 (3;2–4)	2.7 ± 0.8 (3;2–3)	0.593[a]
Parameters of myocardial protection efficacy [7, 10]			
Postoperative MI	1 (1.8)	5 (10.0)	0.075[b]
Atrial fibrillation *de novo*	11 (20.4)	14 (28.0)	0.496[b]
Inotropic support	5 (9.3)	6 (12.0)	0.893[b]
cTnI > 8.5 μg/L/24 h	2 (3.7)	4 (8.0)	0.604[b]
Prolonged MV > 24 h	0 (0)	0 (0)	/
ICU-LOS (days)	2.8 ±1.8 (2.0; 2.0–3.0)	3.4 ± 4.3 (2.0; 2.0–3.0)	0.395[c]
Prolonged ICU-LOS > 3days	8 (14.8)	12 (24.0)	0.348[b]
Hospital (H) LOS (days)	7.7 ± 3.9 (7.0; 6.0–8.0)	8.0 ± 4.5 (7.0; 6.0–7.0)	0.811[c]
Prolonged H-LOS > 10 days	4 (7.4)	6 (12.0)	0.645[b]
30-day mortality	0 (0)	0 (0.0)	/
PMPE	20 (37.0)	28 (56.0)	0.053[b]

***Note*: Results are given as mean ± standard deviation (median; interquartile range) or number (percentage).**

LV – left ventricular; LVEF – LV ejection fraction (Simpson's method); CKD – chronic kidney diseases; GFR – glomerular filtration rate; Diseassed vessels – coronary stenosis > 70%; Euro score – European System for Cardiac Operative Risk Evaluation; MI – myocardial infarction; ICU – intensive care unit; LOS – length of stay; MV – mechanical ventilation;; PMPE – parameters of myocardial protection efficacy.

[a]*t* test; [b]χ^2 test; [c]Mann-Whitney U test.

surgery. Comparison between the groups in terms of PMPE showed a lower rate in the Custodiol® group than in the ST. Thomas M group (37.0% vs. 56.0%, respectively), which was very close to being statistically significant ($p = 0.053$) (Table 4).

Discussion

Myocardial injury is an inevitable consequence of cardiac surgery and cardioplegic arrest is the most preferable technique of intraoperative myocardial preservation. There have been numerous studies comparing the effectiveness of myocardial preservation between a wide variety of blood and crystalloid cardioplegia. However, their relative benefits are still a matter of an on-going debate [4, 8].

Our study compared two strategies of myocardial protection: one using Custodiol® and the other using modified St. Thomas cardioplegia. The difference between the studied groups according to the predictors of perioperative myocardial injury [6] and postoperative cTnI elevation [7] was not significant except in the case of aortic cross clamp (ACC) time and trimetizidine therapy. In particular, we observed a significantly longer ischemic period, with trends to significantly longer CBP time in the Custodiol® group and significantly higher perioperative use of trimetizidine a proven cardioprotective agent [9] in the St.Thomas group. Hypertrophied myocardium, which is much more difficult to protect, was considerably more common in the Custodiol® group, although without statistical significance. These could have an adverse effect on outcomes in the Custodiol® group.

Meta-analysis conducted by Edelman et al. [10] compared Custodiol® with other conventional crystalloid or blood cardioplegia, with regard to myocardial protection, summarizing fourteen comparative studies, and concluded that there was no difference in hospital mortality between Custodiol® and other conventional cardioplegia.

Our study showed no mortality, and the reason could be a low preoperative EuroScor II, and infrequent severe myocardial damage, according to relatively low cardiac enzymes levels. Spontaneous rhythm recovery after ACC is commonly used as an indicator of myocardial protection, ranging from 10% to 99% [11]. Meta-analysis by Edelman et al. [10] presented statistically significant higher rate of

ventricular fibrillation in Custodiol® groups (Custodiol® 20.1% vs. 9.7% in other groups). In our study spontaneous rhythm restoration rate was higher in the Custodiol® group, 31.5% vs. 20.0% in the St Thomas group, but without statistical significance ($p = 0.267$). No significant difference in the rates of postoperative MI, AF, low cardiac output with inotropic support between groups was found in our study, in agreement with the meta-analysis [10]. We observed five times more frequent MI in the Custodiol® group with a trend to statistical significance ($p = 0.075$). In the meta-analysis cross-clamp time was around 60 minutes in both groups and cardiac enzyme levels (CKMB and cTnI) did not differ between groups. The cross-clamp time in our study was under 50 minutes, with comparable enzyme levels between the groups.

There are only few studies in the literature that compared myocardial protection between Custodiol® and St. Thomas cardioplegia [12–16]. These studies discovered no significant difference between the two groups in terms of mortality, however, their findings on myocardial protection in terms of other specific indicators varied in a fashion which seems to suggest that benefits of Custodiol® cardioplegia becomes more pronounced with longer ACC. In the study by Arslan et al. [12], which involved shorter clamping time (less than 40 min), the only significant difference found was longer time to cardiac arrest in the Custodiol® group than in the St. Thomas group (63 vs. 54 seconds, respectively) that could be a disadvantage because it causes more ischemic-reperfusion damage [10, 12]. On the other hand, time to cardiac arrest in our study was about 60 seconds for both groups, whereas ACC time was about 40–50 min. Demmy et al. [13] demonstrated lower defibrillation rate after ACC (64% vs. 91%), but a significantly higher peak level of cTnI 6 hours after surgery in the Custodiol® group (no information about ACC time was given). Hamed et al. [14], in a study with ACC time mean value of about 60 min, showed that St. Thomas cardioplegia was comparable to that of Custodiol® and blood cardioplegia in pediatric cardiac surgery**.**

Careaga et al. [15] demonstrated improved myocardial protection in adult cardiac surgery with Custodiol® cardioplegia according to all considered indicators at myocardial ischemic time longer than 60 min. Lin et al. [16] demonstrated superiority of Custodiol® cardioplegia in complex pediatric cardiac surgery with ischaemic time over 150 min [16]. In our study cross-clamp time was below 50 min in both groups, although significantly longer in the Custodiol® group, and myocardial protection was comparable between the groups.

cTnI and CK-MB are routinely used to evaluate the degree of myocardial damage associated with cardiac surgery. cTnI has been shown to be the most sensitive biochemical marker of intraoperative myocardial injury and is therefore an valuable indicator of the quality of myocardial protection [7, 17]. It has shown that in uncomplicated cardiac surgery, there is an early increase of cTnI around 6 hours post surgery, followed by a rapid decrease, falling down to substantially lower concentrations at 24 hours. A later release of cTnI is more indicative of severe myocardial damage. The unfavorable outcome is indicated if cTnI peaked > 8.5 µg/L 24 hours post surgery [17–19]. Postoperative release of cardiac enzymes in our study over 48 hours, reached peaked values of around 5 µg/L at 6 hours post surgery in each group, indicating a lesser perioperative myocardial damage. This result is in accordance with previous studies [12–14]. PMPE variable revealed a higher rate of adverse outcomes of poor myocardial protection in the St.Thomas M group, very close to statistical significance ($p = 0.053$).

Conclusion

Custodiol® is safe and as effective as conventional cold crystalloid modified St.Thomas cardioplegia for myocardial protection in CABG surgery. The considerably less frequent MI, with a trend towards statistical significance, despite the significantly longer cross-clamp time in the Custodiol® group may suggest that its benefits even in operations with shorter ischemic time could be ascertained in a larger study.

R E F E R E N C E S

1. *Malbouisson LM, Santos LM, Auler JO Jr, Carmona MJ*. Myocardial protection in cardiac surgery. Rev Bras Anestesiol 2005; 55(5): 558–74. (Portuguese)
2. *Gunnes S, Jynge P*. Fundamentals of the Past: Cardioplegia: The First Period Revisited. In: *Podesser BK, Chambers DJ*, editors. New Solutions for the Heart. Wien: Springer-Verlag; 2011. p.15–40.
3. *Veljović M, Popadić A, Vukić Z, Ilić R, Trifunović Z, Antunović M*, et al. Myocardial protection during elective coronary artery bypasses grafting by pretreatment with omega-3 polyunsaturated fatty acids. Vojnosanit Pregl 2013; 70(5): 484–92.
4. *Angeli E, Lueck S, Gargiulo GD*. Different strategies of myocardial protection: the age of perfectionism. J Thorac Dis 2018; 10(3): 1211–3.
5. *Preusse CJ*. Custodiol cardioplegia: a single dose hyperpolarizing solution. J Extra Corpor Technol 2016; 48(2): P15–P20.
6. *Thielmann M, Sharma V, Al-Attar N, Bulluck H, Bisleri G, Bunge JJH,* et al. ESC Joint Working Groups on Cardiovascular Surgery and the Cellular Biology of the Heart Position Paper: Peri-operative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery. Eur Heart J 2017; 38(31): 2392–407.
7. *Januzzi JL Jr*. Troponin Testing After Cardiac Surgery. HSR Proc Intensive Care Cardiovasc Anesth 2009; 1(3): 22–32.
8. *Onorati F, De Feo M, Mastroroberto P, Cristodoro L, Pezzo F, Renzulli A*, et al. Determinants and prognosis of myocardial damage after coronary artery bypass grafting. Ann Thorac Surg 2005; 79(3): 837–45.
9. *Dézsi CA*. Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. Am J Ther 2016; 23(3): e871–9.
10. *Edelman JJ, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P*, et al. Custodiol for myocardial protection and preservation: a systematic review. Ann Cardiothorac Surg 2013; 2(6): 717–28.

11. *Elwatidy AM , Fadalah MA, Bukhari EA, Aljubair KA, Syed A, Ashmeg AK*, et al. Antegrade crystalloid cardioplegia vs antegrade/retrograde cold and tepid blood cardioplegia in CABG. Ann Thorac Surg 1999; 68(2): 447–53.
12. *Arslan A, Sezgin A, Gultekin B, Ozkan S, Akay T, Uguz E,* et al. Low-Dose Histidine-Tryptophan-Ketoglutarate Solution for Myocardial Protection. Transplant Proc 2005;37(7): 3219–22.
13. *Demmy TL, Molina JE, Ward HB, Gorton ME, Kouchoukos NT, Schmaltz RA*, et al. Custodiol versus Plegisol: A phase 3 multicentre myocardial protection study. Int J Angiol 2008; 17(3): 149–53.
14. *Hamed MA, Abdel-Ghaffar RA*. Comparative Study between Three Solutions for Cardioplegia in Pediatric Cardiac Surgery: Histidine-Tryptophan-Ketoglutarate (HTK) Solution, Blood Cardioplegia and Crystalloid (St. Thomas) Cardioplegia. J Anesth Clin Res 2018; 9(4): 818.
15. *Careaga G1, Salazar D, Téllez S, Sánchez O, Borrayo G, Argüero R.* Clinical impact of histidine-ketoglutarate-tryptophan (HTK) cardioplegic solution on the perioperative period in open heart surgery patients. Arch Med Res 2001; 32(4): 296–9.
16. *Lin YZ , Huang JB , Li XW , Tang XM , Lu WJ , Wen ZK* , et al. Clinical comparative analysis of histidine-tryptophan-ketoglutarate solution and St. Thomas crystalloid cardioplegia: A 12-year study from a single institution. Exp Ther Med 2017; 14(3): 2677–82.
17. *Holmvang L, Jurlander B, Rasmussen C, Thüs JJ, Grande P, Clemmensen P*. Use of biochemical markers of infarction for diagnosing perioperative myocardial infarction and early graft occlusion after coronary artery bypass surgery. Chest 2002; 121(1): 103–11.
18. *Benoit MO, Paris M, Silleran J, Fiemeyer A, Moatti N*. Cardiac troponin I: its contribution to the diagnosis of perioperative myocardial infarction and various complications of cardiac surgery. Crit Care Med 2001; 29(10): 1880–6.
19. *Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G*, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. Circulation 2006; 114(14): 1468–75.

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