Int Cardiovasc Res J.2020;**14**(3):95-101.icrj.104728

International Cardiovascular Research Journal

www.ircrj.com

# Comparing the Myocardial Protection of Custodiol Alone and in Combination with Modified Del Nido in Patients Undergoing Cardiac Surgery; A Double-Blind Randomized Clinical Trial

Neda Reihanifard [1], Mohammad Hassan Nemati [2, *], Seyed Hedayatollah Akhlagh [3], Ali Mohammad Keshtvarz Hesam Abadi [4]

[1] Student Research Committee of Shiraz University of Medical Sciences, Shiraz, IR Iran
[2] Department of Surgery, Section of Cardiac Surgery, Shiraz University of Medical Sciences, Shiraz, IR Iran
[3] Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran
[4] Clinical Research Development Center of Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

ARTICLE INFO

*Article Type:*
Research Article

*Article History:*
Received: 8 May 2020
Revised: 2 Aug 2020
Accepted: 15 Aug 2020

*Keywords:*
Myocardium
Troponin
Cardioplegic Solution

ABSTRACT

**Background:** Coronary Artery Bypass Grafting (CABG) has been considered as the complete treatment of Ischemic Heart Disease (IHD). Cardioplegic (extracellular and intracellular) solutions have been suggested to reduce the cross-clamping duration. It was hypothesized that the combination of the two intra- and extra-cellular solutions, namely Del Nido (DN) and custodiol, could result in beneficiary clinical and economic outcomes.

**Objectives:** The present study aimed to compare the myocardial protection of custodiol alone and in combination with modified DN in patients undergoing cardiac surgery.

**Methods:** This prospective, double-blind, clinical trial was conducted on 50 patients undergoing redo CABG surgery. Aortic clamping was performed using custodiol (20 cc/kg) in group A. In group B, custodiol 1000 cc was combined with 15 cc/kg cold DN and was injected using the antigrade method. The two groups were compared regarding the levels of Creatinine Kinase-MB (CK-MB) and troponin at the time of anesthesia induction and two hours and 48 hours after the surgery, intraoperative and postoperative variables, and 48–hour mortality rate.

**Results:** The results showed similar CK-MB levels in the two groups at the induction time ($P = 0.12$). However, a significant difference was observed between the two groups in this regard two hours ($P = 0.018$) and 48 hours after the surgery ($P = 0.021$). Within-group comparisons revealed significant changes in CK-MB and troponin levels in both groups, with a steep increase from induction until two hours after the surgery and a decrease from two hours until 48 hours after the surgery ($P < 0.001$). The results indicated no significant difference between the two groups regarding CK-MB and troponin levels, frequency of intraoperative and postoperative dysrhythmia, need for intraoperative defibrillation, ischemic time, and 48-hour mortality rate ($P > 0.05$). However, the costs were two-folds higher in group A than in group B ($P < 0.001$).

**Conclusions:** The present study findings showed that the selected solution was appropriate in terms of clinical aspects for the patients undergoing CABG surgery with long surgical duration or low Ejection Fraction (EF) and reduced the costs to half. Considering the significant difference in the CK-MB level and the lower troponin level in the combined group (not statistically significant), further studies are required to confirm the clinical priority of the combined solution.

## 1. Background

Cardiovascular disease is the most common underlying cause of death worldwide, which is responsible for about one-third of global deaths (1). In order to prevent the progression of Ischemic Heart Disease (IHD) to Myocardial Infarction (MI) and Cerebrovascular Accident (CVA), revascularization procedures, such as Coronary Artery Bypass Grafting (CABG) and Percutaneous Coronary

*Corresponding author: Mohammad Hassan Nemati, Department of Surgery, Section of Cardiac Surgery, Shiraz University of Medical Sciences, Shiraz, Iran, Cellphone: +98-9171111417,
Email: mohammadhassannemati@gmail.com.

Intervention (PCI), have been suggested, with the former being considered as the durable and complete treatment of IHD (2). Despite the benefits of CABG considering patients' survival and ventricular function, it may be associated with several complications, which can increase the patients' mortality rate (3). One of the main causes of the postoperative complications of CABG is ischemic/reperfusion injury, resulting from the deprivation of the myocardium from blood and oxygen, especially during cross-clamping and abrupt re-oxygenation, which causes injury through free oxygen radicals and calcium ions and may, consequently, induce arrhythmias, stroke, myocardial dysfunction, and multi-organ dysfunction (4). Hence, research has been focused on cardioprotective strategies to reduce the patients' morbidity and mortality rates (5). As a result, a variety of cardioplegic solutions has been suggested to reduce the cross-clamping duration and to allow prolongation of ischemic arrest for complex procedures (6, 7). The two major types of cardioplegic solutions include extracellular solutions (with high potassium, magnesium, and bicarbonate concentrations) and intracellular solutions (with intracellular electrolytes), with the latter providing a longer clamp time (8).

Del Nido (DN) is a unique extracellular cardioplegic solution introduced by Pedro DN and his team in 1990. This solution contains crystalloid/blood at a ratio of 4:1 and can provide a long depolarized diastolic arrest with promising results observed in various cardiac procedures (9-11). However, the available evidence is not clear yet, and research is being continued on its clinical and economic efficacy (12). On the other hand, custadiol, or Histidine-Tryptophan-Ketoglutarate (HTK) crystalloid solution, which was described by Bretschneider in the 1970s is a single-dose intracellular cardioplegic solution with beneficiary effects on myocardial and endothelial functions in CABG (13). Although studies have compared the efficacy of different cardioplegic solutions to suggest the most efficient one (14, 15), none has compared the combination of DN and custodiol, as far as we are concerned. It was hypothesized that the combination of the two intra- and extra-cellular solutions, namely DN and custodiol, could result in beneficiary clinical and economic outcomes.

## 2. Objectives

The present study aims to compare the effects of custodiol alone and in combination with modified DN on myocardial protection and postoperative outcomes of patients undergoing cardiac surgery.

## 3. Patients and Methods

### *3.1. Study Design*

This double-blind, randomized clinical trial was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1398.124) and was registered in the Iranian Registry of Clinical Trials (code: IRCT20190411043239N1). Based on the results of a pilot study and considering the power of 81%, the study sample size was calculated as 20 patients in each group. Considering the probability of loss, the final sample size was raised to 50 patients.

Candidates of redo CABG, CABG + valve replacement, and CABG + Ejection Fraction (EF) < 30% who were scheduled at Shiraz MRI Hospital and Ordibehesht Hospital from 06 May 2018 to 10 Jul 2019 were enrolled into the study. At first, the research objectives and steps were explained to the participants and they were asked to read and sign the written informed consent forms. They were informed that their participation in the study was voluntary and that they were free to leave the study whenever they wished to. Any patient who underwent emergency surgery, had a recent MI event, or had renal failure was not included in the study. The participants were categorized into two groups using a randomization table with a block size of 2 × 25. The medical staff who took blood samples from the patients, administered the cardioplegic solutions, or analyzed the results at the laboratory were blind to the group allocations.

The patients in both groups received 500 – 800 cc ringer lactate, 100 u/kg heparin, and 20% albumin as the prime solution during cardiopulmonary bypass. General anesthesia was induced and maintained. Then, the patients were intubated and central venous catheter and arterial lines were placed. Heparin was prescribed by the anesthetic specialist at a dose of 300 U/kg. After sternotomy, cannulation was performed by the surgeon and a Cardiopulmonary Bypass (CPB) device was attached. After that, venous and aortic clamping was performed in both groups. Based on the randomization code, the patients were considered for aortic clamping by either 1600 cc custodiol (20cc/kg) during six-eight minutes (group A) or the cardioplegic solution of custodiol (1000 cc during four-five minutes) combined with 500 – 600 cc (15cc/kg) cold DN (group B) injected using the antigrade method. Simultaneously, the patients' temperature was decreased to 32-34oC. Near the end of the surgery, the patients were warmed. Detachment of the patients from CPB was performed using the standard protocol. Inotropic agents were prescribed based on the patients' underlying diseases and hemodynamics. Then, the sternum was closed using wire, the skin and the subcutaneous tissue were sutured, and the patient was transferred to the Intensive Care Unit (ICU).

A checklist was designed by the researcher in order to complete the patients' data. The patients' age, sex, blood group, height, weight, baseline hematocrit, and EF were recorded. The primary outcome in the present study was the serum levels of troponin and Creatinine Kinase-MB (CK-MB) measured at the time of anesthesia induction and two hours and 48 hours after the surgery. Troponin I level was measured by VIDAS PC using Biomerius kits and was analyzed using Enzyme-Linked Fluorescence Assay (ELFA). In addition, CK–MB level was measured by Hitachi 717 and Audit kits and was analyzed using the anti CK–M immune–inhibition kinetic UV method. The secondary outcomes were CPB and ischemic times, CPB diuresis, and preoperative and ICU inotrope requirement. Intraoperative and postoperative dysrhythmia and the need for intraoperative defibrillation were also measured at the time of anesthesia induction and two hours and 48 hours after the surgery. The 48-hour mortality rate was also

recorded and compared between the two groups.

*3.2. Statistical Analysis*

The collected data were analyzed using the IBM SPSS Statistics for Windows, version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp.). First, the data were described and then, inferential statistics were used for comparison of the study groups with respect to the study variables. The qualitative variables were described by frequency (percentage), and the two groups were compared regarding the frequency of the variables using chi-square test. For numerical variables, Kolmogorov–Smirnov test was first used to assess the normal distribution of the data. Mean ± Standard Deviation (SD) and/or Standard Error (SE) were reported in case of normal distribution of the data. Comparison of the study groups concerning numerical variables was performed using t-test when the data had normal distribution and using Mann–Whitney U test when the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups, like ischemic time and CPB time. Within-group comparison of the trend of changes in variables measured at different intervals was performed using the Friedman test. Finally, the associations between the variables were tested by Pearson's or Spearman's correlation coefficient. In all tests, $P < 0.05$ was considered to be statistically significant.

## 4. Results

A total of 25 patients were studied in each group (Figure 1). Comparison of the two groups' demographic and baseline characteristics, as shown in Table 1, indicated similar sex distribution, blood groups, mean age, height, weight, baseline hematocrit, and EF ($P > 0.05$).

The mean ± SD of ischemic time was 72.52 ± 33.61 minutes in group A and 71.20 ± 19.83 minutes in group B ($P = 0.866$). The mean ± SD of CPB time was 108.40 ± 34.20 minutes in group A and 117.12 ± 36.60 minutes in group B ($P = 0.388$).

The results revealed no significant difference between the two groups regarding CK–MB level at the induction time ($P = 0.12$). However, a significant difference was observed between the two groups in this regard two hours ($P = 0.018$) and 48 hours ($P = 0.021$) after the surgery. In the meantime, no significant difference was observed between the two groups concerning troponin level at any of the three intervals (induction and two hours and 48 hours after the surgery, $P > 0.05$; Table 1). Yet, the trend of changes for CK–MB and troponin levels was significant in both groups ($P < 0.001$ for both). Accordingly, CK–MB and troponin levels followed a steep ascending trend from induction until two hours after the surgery and a decreasing trend from two hours until 48 hours after the surgery in both groups ($P < 0.001$ for both; Table 2). Comparison of the two groups showed no significant difference in CK–MB level at the three intervals ($P > 0.05$; Table 2). Within-group comparison of the differences in the mean values of troponin showed a significant difference in group A at all three intervals ($P < 0.001$, $P = 0.049$, and $P < 0.001$, respectively). Nonetheless, a significant difference was detected in this regard in group B from induction until two hours and 48 hours after the surgery ($P < 0.001$ for both), but not from two hours until 48 hours after the surgery ($P = 0.359$; Figure 2). Furthermore, comparison of the differences in troponin levels showed no significant difference between the two groups in this regard ($P > 0.05$; Table 2).

The results of Spearman's correlation coefficient showed no significant association between EF and troponin levels

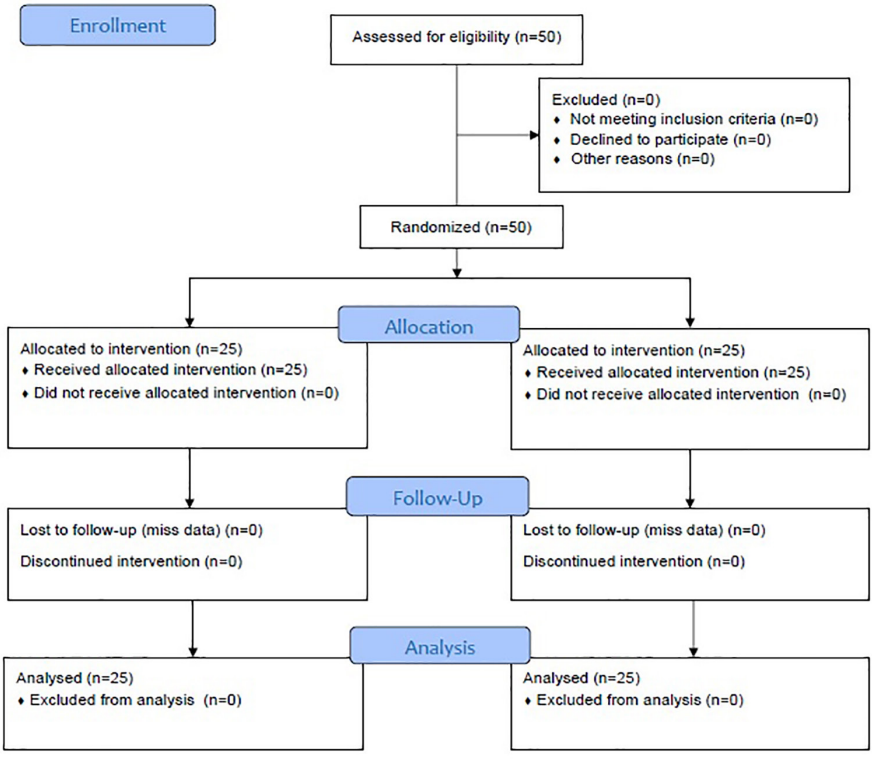


**Figure 1.** Flow Diagram for Inclusion of the Patients in Each Study Step

**Table 1.** Comparison of the Two Groups Regarding Demographic and Baseline Characteristics

| Variables | Categories | Groups | | P-value |
|---|---|---|---|---|
| | | Combined group | Custodiol group | |
| Sex, Number (percentage) | Male | 21 (84%) | 4 (16%) | 0.713 [a] |
| | Female | 20 (20%) | 5 (4%) | |
| Blood group | A | 8 (32%) | 4 (16%) | 0.416 [a] |
| | B | 9 (36%) | 11 (44%) | |
| | O | 8 (32%) | 10 (40%) | |
| | AB | 0 | 0 | |
| Age (years), mean ± SD | | 65.56 ± 9.98 | 66.16 ± 6.64 | 0.804 [b] |
| Height (cm), mean ± SD | | 169.32 ± 10.01 | 166.60 ± 7.44 | 0.281 [b] |
| Weight (kg), mean ± SD | | 74.52 ± 14.41 | 72.84 ± 15.70 | 0.695 [b] |
| Baseline hematocrit (%), mean ± SD | | 34.89 ± 8.59 | 35.10 ± 4.59 | 0.916 [b] |
| Baseline ejection fraction (%), mean ± SD | | 44.52 ± 10.62 | 38.76 ± 12.96 | 0.092 [b] |

[a] The results of chi-square test, [b] the results of Mann-Whitney U test; all tests were considered as statistically significant at $P < 0.05$

**Table 2.** Comparison of the Two Groups Regarding CK-MB and Troponin Values

| CK–MB | Group A | Group B | P-value |
|---|---|---|---|
| CK–MB level at induction (IU/L), mean ± SD | 18.27 ± 16.21 | 16.03 ± 5.96 | 0.121 |
| CK–MB level two hours after the surgery (IU/L), mean ± SD | 86.09 ± 53.50 | 56.77 ± 20.19 | 0.018 |
| CK–MB level 48 hours after the surgery (IU/L), mean ± SD | 25.88 ± 16.40 | 16.70 ± 9.06 | 0.021 |
| CK–MB difference between two hours after the surgery and baseline (IU/L), mean ± SD | 68.50 ± 51.89 | 41.54 ± 19.80 | 0.13 |
| CK–MB difference between 48 hours after the surgery and two hours after the surgery (IU/L), mean ± SD | 60.50 ± 44.36 | 40.23 ± 19.56 | 0.16 |
| CK–MB difference between 48 hours after the surgery and baseline (IU/L), mean ± SD | 12.86 ± 13.94 | 8.33 ± 5.86 | 0.47 |
| Troponin | | | |
| Troponin level at induction (ng/mL), mean ± SD | 27.56 ± 20.82 | 33.21 ± 20.34 | 0.337 |
| Troponin level two hours after the surgery (ng/mL), mean ± SD | 4723.54 ± 2400.99 | 4081.73 ± 2178.02 | 0.327 |
| Troponin level 48 hours after the surgery (ng/mL), mean ± SD | 2324.43 ± 1890.42 | 2769.81 ± 2241.29 | 0.451 |
| Troponin difference between two hours after the surgery and baseline (ng/mL), mean ± SD | 4695.97 ± 2398.96 | 4048.51 ± 2173.54 | 0.322 |
| Troponin difference between 48 hours after the surgery and two hours after the surgery (ng/mL), mean ± SD | 3009.49 ± 2172.12 | 2536.83 ± 2039.25 | 0.456 |
| Troponin difference between 48 hours after the surgery and baseline (ng/mL), mean ± SD | 2296.87 ± 1895.89 | 2736.59 ± 2231.40 | 0.432 |
| Urinary output at induction (ng/mL), mean ± SD | 209.09 ± 173.6 | 333.33 ± 188.041 | 0.024 |
| Urinary output two hours after the surgery (ng/mL), mean ± SD | 365.12 ± 193.87 | 371.60 ± 167.94 | 0.901 |
| Urinary output 48 hours after the surgery (ng/mL), mean ± SD | 171.40 ± 128.89 | 201.66 ± 164.04 | 0.489 |
| Urinary output difference between two hours after the surgery and baseline (ng/mL), mean ± SD | 210.61 ± 170.30 | 172.50 ± 107.630 | 0.384 |
| Urinary output difference between 48 hours after the surgery and two hours after the surgery (ng/mL), mean ± SD | 215.54 ± 146.66 | 194.16 ± 104.66 | 0.576 |
| Urinary output difference between 48 hours after the surgery and baseline (ng/mL), mean ± SD | 132 ± 120.55 | 198.69 ± 165.2 | 0.135 |

Abbreviations: CK-MB, creatinine kinase-MB

at two hours ($P = 0.637$) and 48 hours ($P = 0.116$) after the surgery. However, a significant relationship was observed between the troponin levels at two hours and 48 hours after the surgery ($r = 0.386$, $P = 0.006$).

The mean ± SE of the total urinary CPB diuresis was 650.00 ± 99.87 cc in group A and 814.00 ± 123.00 cc in group B, but the difference was not statistically significant ($P = 0.375$). The changes in the urinary output showed a descending trend from the induction time until two hours after the surgery ($P = 0.636$) and an ascending trend from two hours until 48 hours after the surgery ($P = 0.001$; Table 2).

The frequency of dysrhythmia was 8% (n = 2) in group A and 4% (n = 1) in group B at induction ($P = 0.552$), 20% in group A (n = 5) and 4% in group B (n = 1) two hours after the surgery ($P= 0.082$), and 24% in group A (n = 6) and 8% in group B (n = 2) 48 hours after the surgery ($P = 0.123$). Moreover, 18 patients in group A (72%) and 13 patients in group B (52%) required inotropes during the surgery ($P = 0.145$). This measure was obtained as 11 patients in each group during the ICU admission ($P = 1.00$). In addition, postoperative defibrillation was required for two patients in group B (8%; one lidocaine and one Direct Current (DC) shock) and no patients in group A ($P = 0.353$). Furthermore, there were three cases of death within 48 hours in group A (12%) and no cases in group B ($P = 0.074$). Finally, the costs of the cardioplegic solution were two-folds higher for group A in comparison to group B (2,000,000 Tomans [about 476 USD] in group A and 1,000,000 Tomans [about 238 USD] in group B; $P < 0.001$).

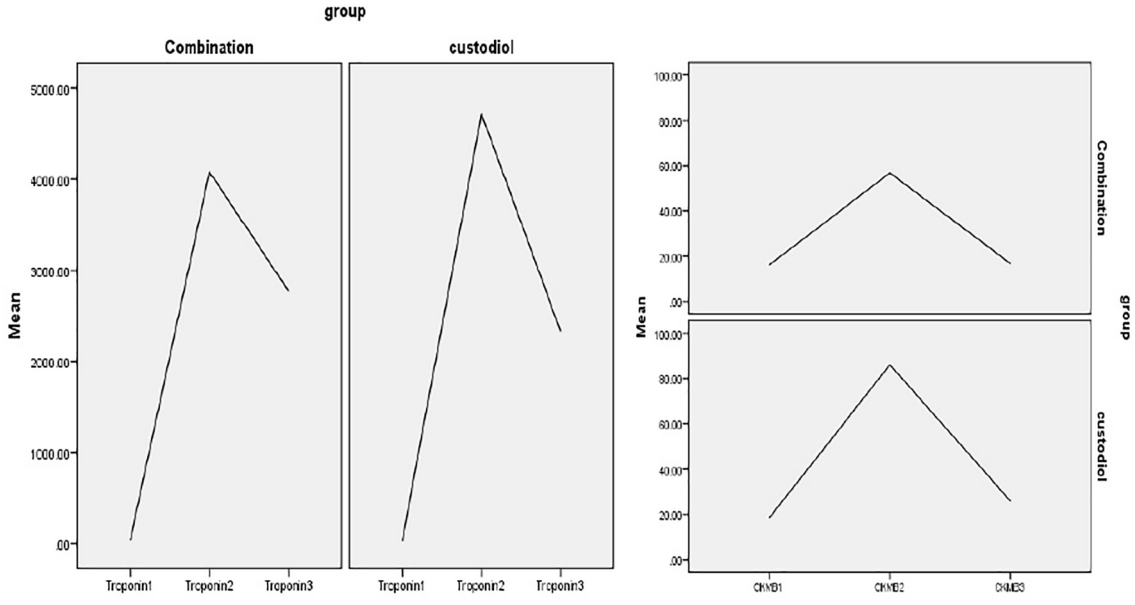


**Figure 2.** The Trend of Changes in Creatinine Kinase-MB and Troponin Levels in the Two Study Groups

## 5. Discussion

In the present study, comparison of two methods of cardioplegic injection (20 cc/kg custodiol or 1000 cc custodiol combined with 15 cc/kg cold DN) in two groups of 25 patients with similar demographic characteristics showed similar ischemic and CPB times in the groups. These results indicated that both cardioplegic solutions had similar effects on the durations of ischemia and CPB. Ischemic and CPB times are both important in terms of myocardial injury during CABG; CPB is associated with the risk of Acute Kidney Injury (AKI) (16) and aortic cross clamp time > 60 minutes is considered as an independent predictor of patients' mortality and major morbidity rates after cardiac surgery (17). Although the mean ischemic time of both groups in the present study was > 60 minutes, it was shorter than 90 minutes, which is considered high-risk and requires additional interventions. Comparison of the mean values of ischemic and CPB times in group A to those reported in the previous studies comparing custodiol to other cardioplegic agents showed a shorter mean ischemic time in the present study. In the study by Viana et al., a single dose of custodiol (25 cc/kg) was administered to 126 adult patients undergoing cardiac procedures during five–seven minutes. The results indicated that the mean ischemic time was 153 ± 66 minutes and the mean CPB time was 215 ± 98 minutes (18), both of which were about two folds greater than those of group A receiving custodiol alone, while the administered dose in the present study was lower than that used in the study by Viana et al. (18). This difference could be attributed to the different details during cardiac procedures, including the type of surgery and number of grafts, which have a significant effect on ischemic and CPB times based on the results of the present study and those of the previous studies (19).

In the present study, the effect of the combination of custodiol and DN was measured, while the previous studies mainly compared the efficacy of DN alone (20, 21). Guajardo et al. reported that the mean CPB time was 65 ± 21 minutes and the mean ischemic time was 52 ± 20 minutes in patients undergoing CABG with the administration of a single dose of DN (22), which seemed shorter compared to group B in the present study. In the study by Kim and colleagues, using 1000 – 1500 cc DN resulted in the mean aortic cross-clamp time of 97 ± 42 minutes in the DN group in the adults undergoing cardiac surgical procedures and 88 ± 42 minutes in the patients undergoing CABG (20), both of which seemed longer than the mean ischemic time in group B in the present study (72.52 ± 33.61 minutes). Moreover, Sorabella et al. reported that the mean ischemic time was 61.3 ± 18.9 minutes in adult patients undergoing preoperative aortic valve surgery (21), which seemed shorter than that found in the present study. The difference among the results could result from different administration protocols used for DN.

In the current study, CK–MB level was higher in group A than in group B two hours and 48 hours after the surgery, which suggested the superiority of the combination of the cardioplegic solutions compared to custodiol alone in terms of myocardial injury. Nevertheless, no significant difference was observed between the two groups concerning troponin levels at the three intervals as well as the change in CK–MB and troponin levels. Longer ischemic time has been associated with a higher level of troponin in patients undergoing valve surgery with the use of DN (23). A review of five studies reporting CK–MB and troponin levels in patients after CABG indicated no significant difference between the groups receiving custodiol and those receiving conventional cardioplegia (15). However, no studies reported its difference from the combined solution of DN + custodiol, as reported in the present study. The current study findings also showed no significant difference in the urinary output within 48 hours after the surgery, which was indicative of the renal function of the study groups. AKI is an important complication after CABG and can represent long ischemic time and injury to sensitive organs, like kidneys (24). The results of the present study showed no significant difference between the two groups in this regard.

The present study results revealed no significant difference between the two groups regarding the frequency of dysrhythmia at the three time points (at induction, two hours after the surgery, and 48 hours after the surgery) and the frequency of defibrillation. Dysrhythmia and the need for defibrillation can be the important predictors of cardiac structural dysfunction after CABG and have been considered as the major causes of morbidity, increased length of hospital stay, and economic costs (25). Comparison of the frequencies reported in the present study to those of the previous reports showed much lower frequencies in the present study (26, 27). Although the difference between the two groups was not statistically significant, there were no cases requiring defibrillation and no cases of death in group B within 48 hours after the surgery, which was clinically important. On the other hand, there were three cases of death in the custodiol group (12%). Other researchers also reported no cases of death among the patients undergoing redo CABG (28), which was in agreement with the results of the present study in the combined group. Nevertheless, the mortality rate and surgical outcome of CABG varied based on the type of surgery, surgical details, and patients' underlying diseases (29, 30).

In the present study, calculation of the direct costs of the cardioplegic solution used in each group showed that the costs of custodiol solution were twice as much as the combined solution, and the difference was statistically significant. Considering the high costs of CABG surgery and hospital stay (31), reducing the patients' costs is an important parameter. The current study results showed the superiority of the combined solution in terms of costs.

One of the limitations of the present study was the limited number of patients in each group and the short follow-up period. Thus, further studies with larger sample sizes are required to get more reliable results.

### *5.1. Conclusion*

The present study findings confirmed that the combination of DN with custodiol was as efficient as custodiol alone and did not increase the myocardial injury or ischemic time, while it could reduce the costs to half. Lack of a significant difference in the mortality rate and postoperative cardiac outcome could result from the few number of patients included in each study group and the short follow-up period. Therefore, future studies are suggested to investigate the effects of this combination in terms of different clinical and prognostic parameters.

### *5.2. Clinical Trial Registration Code*

IRCT20190411043239N1

### *5.3. Ethical Approval*

IR.SUMS.REC.1398.124

**Acknowledgements**

The authors would like to thank the Student Research Committee, the cardiac surgery, and ICU teams.

**Authors' Contribution**

Study concept and design: N.R. and MH.N.; analysis and interpretation of data: N.R. and MH.N.; drafting of the manuscript: N.R.; critical revision of the manuscript for important intellectual content: MH.N., H.A., and N.R.; statistical analysis: AM.K.

**Funding/Support**

This study was supported in part by grant No. 1396-01-01-16139 from Shiraz University of Medical Sciences and by a teaching and research scholarship from Shiraz College of Physicians (Dr. Yones Ghasemi).

**Financial Disclosure**

The authors have no financial interests related to the material in the manuscript.

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