Benefits of custodiol cardioplegia in the context of cardiac surgery training

Ashraf M. Elnahas[a], Basem M. Abdelgawad[a], Mohamed M. Ali[b], Amany N. Khedr[c], Mohamed G. Sobhy[c], Ihab Omar[d]

Departments of [a]Cardiothoracic Surgery, [b]Cardiology, [c]Anesthesia and Intensive Care, Faculty of Medicine, Benha University, Benha, Egypt, [d]Department of Cardiothoracic Surgery, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

Correspondence to Basem M. Abdelgawad, BMA, 15 Hasan Muwafi Street, Hi Elrawdah, New Benha, Qalyobia 13518, Egypt.
Tel: +20 100 871 3556; fax: 0133228631;
e-mail: bassem.abdelgawad@fmed.bu.edu.eg

Received: 24 August 2021
Accepted: 29 August 2021
Published: 20 June 2022

The Egyptian Journal of Surgery 2021, 40:1338–1342

Context
The need for competent surgeons to provide high-quality surgical interventions is crucial. The challenge of worsening the outcome has a great negative impact on the rate of training, especially in complex or long-duration procedures. Custodiol cardioplegia is an attractive solution for many cardiac surgeons, as a single dose provides a long period of myocardial protection.
Aims
We aimed to evaluate the benefit of custodiol cardioplegia in comparison with the conventional one in supporting training programs.
Settings and design
A retrospective study was conducted in the period from March 2016 to January 2021. The study included 240 adult patients who underwent open-heart surgeries and required cardioplegia and cardiopulmonary bypass.
Patients and methods
Patients were divided into two groups: group A (120 patients) received conventional cardioplegia. Group B (120 patients) received custodial cardioplegia.
Statistical analysis used
The patient's data were analyzed using the Statistical Package for Social Sciences (SPSS), version 21 for Windows (SPSS Inc., Chicago, Illinois, USA). Comparison between groups was done by χ^2 test. Quantitative data were presented as mean ±SD. Qualitative data were presented as numbers and percentages. Student *t* test and χ^2 test were used to compare between two groups. A *P* value less than 0.05 was considered statistically significant.
Results
The preoperative patient characteristics were comparable among both groups regarding the demographic data, the comorbidities, and cardiac parameters. There was a significant difference between both groups in cross-clamp (133.35 vs. 124.81 min) and total bypass (162.41 vs. 154.7 min) times ($P<0.001$). The mechanical ventilation, intensive care, and hospital stay times were significantly prolonged in the conventional group ($P<0.05$). The 30-day mortality was lower in the custodial group but was not significant ($P=0.207$).
Conclusion
The use of custodiol is more effective than cold cardioplegia in protecting the myocardium and thus supporting training programs.

Keywords:
coronary artery bypass grafting, cold-blood cardioplegia, custodial, histidine–tryptophan–ketoglutarate solution

Egyptian J Surgery 40:1338–1342

1110-1121

Introduction

Surgical training aims to produce competent surgeons that can deliver the highest quality of surgical care. However, many challenges negatively impact the training process and subsequently affect this outcome, unless certain changes are made [1].

The nonsufficient opportunity for trainees to practice represents a major challenge to residency programs. The efforts made by Ericsson [2] on the production of expertise have shown that expert surgeons develop because of continued 'deliberate practice' over the years. Deliberate practice involves performing specific tasks focusing on improving the performance, associated with a detailed assessment, and the opportunity to refine performance through repeating the tasks.

The fear of compromising patient safety and decreasing the efficiency in operating-room time resulted in less time for training and practicing during surgical procedures [3]. Therefore, the introduction of

custodiol was an attractive solution for many surgeons because it is administered as a single dose and has the potential to protect the myocardium for about 3 h [4].

In the 1970s, Bretschneider described the histidine–tryptophan–ketoglutarate (HTK), or custodiol solution and also known as Bretschneider's solution. It is considered an intracellular type of cardioplegia due to its low calcium and sodium content. The low extracellular sodium causes hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. This is in contrast to the conventional cardioplegic solutions, where the high extracellular potassium causes arrest by membrane depolarization [5].

Patients and methods

Objective

The main aim was to evaluate the choice of cardioplegia type in assisting the training programs by providing better myocardial protection for longer duration with giving the best outcome. Ethics approval of the study protocol was approved by the Ethical Committee of the Faculty of Medicine at Benha University Hospital. Committee's reference number is not applicable. Informed consent was waived due to the retrospective nature of the study.

Study design

A retrospective study was conducted in the period from March 2016 to January 2021. The study included 240 adult patients who underwent open-heart surgeries and required cardioplegia and cardiopulmonary bypass (CPB). Patients were totally operated upon by training surgeons (associate consultants or senior fellows) with either hands-on or observation by a senior consultant. The cardiac center policy shifted to the routine use of HTK cardioplegia since January 2019 and accordingly patients were divided into two groups:

Group A (120 patients) received conventional cardioplegia from March 2016 to January 2019.
Group B (120 patients) received custodial cardioplegia from January 2019 to January 2021.

Inclusion criteria

Patients required isolated on-pump coronary artery bypass grafting or double-valve replacement with prolonged cross-clamp time (CCT) (>100 min).

Exclusion criteria

Minimally invasive approach, patients with advanced cerebral, pulmonary, renal, or hepatic disease, and patients with low left-ventricular ejection fraction (LVEF) less than 50%.

Cardioplegia technique

The body temperature was reduced to 28–30°C and the cardioplegia solution was given in an antegrade fashion.

In group A (conventional cardioplegia): the solution was administered as an initial dose of 15 ml/kg and was repeated every 20–30 min as 10 ml/kg. One liter of the solution contains 20 mmol/l of potassium, 150 mmol/l of sodium, 15 mmol/l of magnesium, 200 mg of lidocaine, and a 4 : 1 blood : crystalloid ratio with cooling to 4°C.

In group B (custodiol): the HTK solution was administered at 4°C at an initial pressure of 80 mmHg. When the heart was arrested, the pressure was maintained at 50–60 mmHg. A single dose of 20 ml/kg was given over 8 min.

Study endpoints

Our primary endpoint was the 30-day mortality. The secondary endpoints were recent myocardial infarction, time of ventilation, length of ICU and hospital stays, intraaortic balloon pump use, need for high inotropic support, readmission to the hospital within 30 days, and postoperative tachyarrhythmia requiring cardioversion.

Results

The mean age in group A was 63.3±7.42 and 61.6±8.51 years for group B without a statistically significant difference (P=0.1). The male/female ratio was 68 (56.7%)/52 (43.3%) and 76 (63.3%)/44 (36.7%) for groups A and B, respectively, with P value of 0.293.

The preoperative data showed that there was no statistically significant difference between both groups regarding comorbidities, New York Heart Association classification, hematocrit, and creatinine levels (Table 1).

The mean total CCT and total CPB time were higher in group A than in group B with a highly significant statistical difference (P<0.0001) as shown in Table 2. Intraoperative events were also compared in the same table, except for ventricular arrhythmia, which was significantly higher in custodial group (P=0.02).

Table 1 Comparison between the two groups' demographics and clinical parameters

	Group A (*N*=120) [*n* (%)]	Group B (*N*=120) [*n* (%)]	*P* value
Hypertension	80 (66.7)	72 (60)	0.284
Diabetes	76 (63.3)	84 (70)	0.271
Smoking	36 (30)	48 (40)	0.105
COPD	8 (6.7)	4 (3.3)	0.238
Dyslipidemia	24 (20)	16 (13.3)	0.164
Myocardial infarction	40 (33.3)	36 (30)	0.575
Cerebrovascular event	8 (6.7)	4 (3.3)	0.238
LVEF %	56.6±7.1	55.7±6.3	0.3
Arrhythmia	31 (25.8)	36 (30)	0.471
Pulmonary hypertension	33 (27.5)	28 (23.3)	0.459
NYHA			
I	4 (6.7)	6 (10)	0.515
II	48 (40)	56 (46.7)	0.298
III	60 (50)	51 (42.5)	0.242
IV	4 (3.3)	1 (0.8)	0.173
Hematocrit (g/dl) (mean±SD)	35.31±5.25	36.42±6.53	0.148
Creatinine (μmol/l) (mean±SD)	0.92±0.36	1.02±0.44	0.056

COPD, chronic obstructive pulmonary disease; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Comparison between the two groups regarding operative data

	Group A (*N*=120) Mean±SD	Group B (*N*=120) Mean±SD	*P* value
TCPBT (mean±SD) (min)	162.41±13.53	154.7±16.62	<0.001
TCCT (mean±SD) (min)	133.35±12.31	124.81±9.51	<0.001
Type of procedure [*n* (%)]			
CABG	92 (76.7)	87 (72.5)	0.459
DVR	28 (23.3)	33 (27.5)	0.459
Arrhythmia after removing the cross-clamp [*n* (%)]			
AF	26 (21.7)	23 (19.2)	0.631
VT/VF	25 (20.8)	41 (34.2)	0.02
CPB weaning failure	9 (7.5)	4 (3.3)	0.152
IABP (intraoperative)	6 (5)	4 (3.3)	0.515

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DVR, double-valve replacement; IABP, intraaortic balloon pump; TCCT, total cross-clamp time; TCPBT, total cardiopulmonary bypass time; VT/VF, ventricular tachycardia/ventricular fibrillation.

Table 3 Operative and clinical outcomes for the studied patients

Variables	Group A (*N*=120)	Group B (*N*=120)	*P* value
ICU stay (days)	4.21±1.87	3.73±1.67	0.037
Clinical cerebral stroke [*n* (%)]	6 (5)	4 (3.3)	0.515
Myocardial infarction [*n* (%)]	8 (6.6)	8 (6.6)	1
Time of ventilation (h)	17.2±6.21	13.8±3.56	< 0.001
Re-exploration for bleeding	12 (10)	8 (6.6)	0.352
Readmission to ICU	2 (1.7)	4 (3.3)	0.406
Hospital stay, days	11.4±4.37	8.8±2.61	<0.001
Early LVEF, % (1–3 days)	42.7±7.84	45±5.51	0.009
Pre-discharge LVEF (%)	55.1±5.2	53.8±6.5	0.1
30-day mortality	11 (9.2)	6 (5)	0.207

LVEF, left-ventricular ejection fraction.

The postoperative outcome was compared in Table 3. The mechanical ventilation, ICU, and hospital-stay times were significantly prolonged in the conventional group ($P<0.05$). The 30-day mortality was lower in the custodial group but not significant ($P=0.207$).

Discussion

The most obvious way for surgical specialties to be an attractive career choice for junior doctors is career progression. Developing a definitive and clear training pathway will be the only way to ensure resident

application to surgical specialties. Therefore, any factor that would facilitate or support surgical training was studied [6].

Dumon *et al.* [7] have demonstrated an increasing pressure to make a surgical specialty more attractive. The education component is considered the essential one. Medical graduates today have a different order of values than those who were graduated 20 years ago. Junior doctors today cite the desire to generate a large income and the lifestyle as the most important influences in choosing a specialty.

No one denies that surgical skills are still learned at considerable expense, including longer operating time, longer hospital stay, more cost, higher rate of complications, and less-than-optimal results [8]. In many institutions like ours, the presence of training programs necessitates giving good chances for fellows to upgrade together without compromising the patient care or outcome. The more the exposure and practicing rate, the better the expected skills developed. However, there are no enough simple cases, with good anatomy, and requiring short ischemic time was available for this purpose. Therefore, thinking of a better myocardial-preservation strategy allowed us to achieve this goal with maintaining the high quality of care even with complex cases. However, we have excluded patients with low LVEF less than 50% to reduce the operative risk and because these cases are not expected to add a different experience to the trainees.

Few studies have compared the use of custodiol and conventional cardioplegia in complex cardiac surgical procedures. This is important because we believe that it is better to evaluate the safety and efficacy of such solutions in cases with prolonged ischemic time.

We have compared the outcomes of two different periods based on the type of cardioplegia. The preoperative patient characteristics were comparable among both groups regarding the age, clinical condition, the prevalence of hypertension, smoking, dyslipidemia, previous myocardial infarction, chronic obstructive pulmonary disease, and New York Heart Association class. Furthermore, the cardiac condition was also comparable, especially regarding the LVEF, the presence of arrhythmia, or pulmonary hypertension.

Our study showed that the custodiol group had a significantly lower both ischemic and CPB time than the conventional group ($P<0.001$). These findings can be explained by the frequent interruptions necessary for the repetitive administration of conventional cardioplegia in contrast to the single dose of HTK solution and the need for more reperfusion time after removing the cross-clamp. Furthermore, the cumulative CCT was prolonged due to a higher incidence of initial weaning failure from CPB.

We have found that the mean CCT required for an average three-graft coronary artery bypass grafting or double-valve replacement is beyond 100 min, which was prolonged enough to reveal ischemic complications. Although statistically nonsignificant, the rate of mortality as a primary outcome was higher in the conventional group ($P=0.207$). The rates of complications were also higher with conventional plegia (Table 3) starting by failure of weaning from CPB, the rate of intraaortic balloon pump use, the need for high inotropic support, prolonged ventilation time, and prolonged ICU and hospital-stay times.

In a similar study by de Haan *et al.* [9] on patients undergoing cardiac surgery with prolonged CCT, the CCT was significantly longer (125.6 vs. 93.1 min; $P<0.001$) in the custodiol than in the St Thomas group. Although they did not find significant differences between the two groups regarding postoperative complications or mortality, they referred this great difference in CCT to surgeon preference and case difference, which give some bias in comparing the types of cardioplegia.

Moreover, Sung *et al.* [10] evaluated the HTK solution on 67 patients who underwent heart transplantation with a mean ischemic time of 152.3 versus 159.6 min for the cold-blood cardioplegia group. The CPB time was less in the HTK group (158.3 vs. 173.9), and the multivariate analyses showed a significant reduction in pumping time in HTK group ($P=0.002$). The length of ICU stay (8.2 vs. 12.2) and hospital stay (37.1 vs. 44.5) was also reduced in the HTK group.

Furthermore, Liu *et al.* [11] have evaluated the efficacy of custodial versus cold cardioplegia in complex pediatric cardiac surgeries where they reported CCT of 172.5 versus 194.2 min, respectively. They measured the level of creatine kinase and was less in the HTK group without significance on day one, and by the second day, it was statistically significant ($P<0.01$). The mortality in the HTK group was also significantly lower ($P<0.05$).

In another similar study but in contrast to our results, Viana *et al.* [12] reported CCT (145 vs. 141 min, $P=0.3$), and the postoperative outcomes were nonstatistically significant for any of the studied endpoints even after propensity-score matching. In particular, the mortality rate (1 vs. 4%, $P=0.63$) in blood versus custodiol group. The incidence of arrhythmia was nearly equal: atrial

fibrillation (23 vs. 25%, P=0.83), heart block (9.9 vs. 4.2%, P=0.34), and ventricular tachycardia/ventricular fibrillation (2.8 vs. 1.2%, P>0.99).

Furthermore, it is difficult to evaluate the outcome of cardioplegia with short ischemic time, such as those reported by the study of Prathanee *et al.* [13] where the number of distal coronary anastomosis more than 4 was 75%, 71.4% in warm-blood versus custodial groups with a mean CCT of 77.55 and 71.22, respectively.

In a systematic review of 14 studies, Edelman *et al.* [14] compared custodiol with conventional cardioplegia in adult cardiac surgery. The mortality risk was similar in the 925 patients who received custodiol plegia and the 911 patients who received the conventional one. Most of these studies did not address the issue of prolonged ischemic time. Furthermore, in five studies evaluating ischemic biomarkers as indicators for myocardial damage, they reported a trend toward shorter CCT in the custodiol and conventional cardioplegia groups (62.9 vs. l 54.8 min, P=0.11). The mean differences for both creatine kinase-MB and troponin I were nonsignificant between groups.Regarding the safety of custodial, we had demonstrated a higher incidence of ventricular arrhythmia that was limited to the declamping period and was controllable. Similarly, many authors reported a significantly higher incidence of ventricular fibrillation with custodiol. However, it occurred also upon declamping and was managed successfully by direct-current shock [14–16].

In this study, early postoperative echo showed significantly poorer LV function in the conventional group (P=0.009), indicating that a single dose of HTK solution provides better myocardial protection than repetitive doses of cold-blood cardioplegia, especially with prolonged ischemic time. However, at discharge, there was no significant difference between survivors of both groups (P=0.1).

Conclusion

The use of custodiol cardioplegia allowed better training opportunity by granting better myocardial protection and better outcome, especially when prolonged ischemic time is indicated.

Limitations of the study

The study was conducted at one cardiac center only. The variation in trainees' skills and learning capabilities was not determined. The learning chances provided by the senior surgeons were personally variable. The outcomes were not analyzed in detail to justify their relation only to myocardial preservation.

Acknowledgements

Authors' contributions: All authors (a) have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (b) have been involved in drafting the paper or revising it critically for important intellectual content; and (c) have given final approval of the version to be published.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Ashmore DL. Strategic thinking to improve surgical training in the United Kingdom. Cureus 2019; 11:e4683.

2 Ericsson KA. Deliberate practice and the acquisition and maintenance of expert performance in medicine and related domains. Acad Med 2004; 79: S70–S81.

3 Sonnadara RR, Mui C, McQueen S, Mironova P, Nousiainen M, Safir O, *et al.* Reflections on competency-based education and training for surgical residents. J Surg Educ 2014; 71:151–158.

4 Bretschneider HJ, Hübner G, Knoll D, Lohr B, Nordbeck H, Spieckermann PG. Myocardial resistance and tolerance to ischemia: physiological and biochemical basis. J Cardiovasc Surg (Torino) 1975; 16:241–260.

5 Hölscher M, Groenewoud AF. Current status of the HTK solution of Bretschneider in organ preservation. Transplant Proc 1991; 23:2334–2337.

6 Harries RL, Williams AP, Ferguson HJ, Mohan HM, Beamish AJ, Gokani VJ. The future of surgical training in the context of the 'Shape of Training' review: consensus recommendations by the association of surgeons in training. Int J Surg 2016; 36 (Suppl 1):S5–S9.

7 Dumon KR, Traynor O, Broos P, Gruwez JA, Darzi AW, Williams NN. Surgical education in the new millennium: the European perspective. Surg Clin North Am 2004; 84:1471–1491.

8 Peracchia A. Presidential address: surgical education in the third millennium. Ann Surg 2001; 234:709–712.

9 de Haan M, van Straten A, Overdevest E, de Jong M, Soliman-Hamad M. Safety of Custodiol cardioplegia: a cohort study in patients undergoing cardiac surgery with elongated aortic cross-clamp time. Perfusion 2020; 35:591–597.

10 Sung SY, Lin CY, Song JY, Tsai YT, Kao CH, Lee CY, *et al.* Myocardial protection in donor heart preservation: a comparison between Bretschneider's histidine-tryptophan-ketoglutarate solution and cold blood cardioplegia. Transplant Proc 2014; 46:1077–1081.

11 Liu J, Feng Z, Zhao J, Li B, Long C. The myocardial protection of HTK cardioplegic solution on the long-term ischemic period in pediatric heart surgery. ASAIO J 2008; 54:470–473.

12 Viana FF, Shi WY, Hayward PA, Larobina ME, Liskaser F, Matalanis G. Custodiol versus blood cardioplegia in complex cardiac operations: an Australian experience. Eur J Cardiothorac Surg 2013; 43:526–532.

13 Prathanee S, Kuptanond C, Intanoo W, Wongbhudha C, Karunasumaeta C. Custodial-HTK solution for myocardial protection in CABG patients. J Med Assoc Thai 2015; 98 (Suppl. 7):S164–S167.

14 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; 2:717–728.

15 Abdelmajeed AM, Kerdany AB, Ibrahim AA, Hameed OA, Soliman AA. Custodiol versus extracellular crystalloid cardioplegia in mitral valve replacement in patients with low ejection fraction. Egypt J Surg 2021; 40:375–379.

16 Mercan I, Dereli Y, Topcu C, Tanyeli O, Isik M, Gormus N, Ozturk EY. Comparison between the effects of Bretschneider's HTK solution and cold blood cardioplegia on systemic endothelial functions in patients who undergo coronary artery bypass surgery: a prospective randomized and controlled trial. Braz J Cardiovasc Surg 2020; 35:634–643.