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Myocardial Protection Using Custodiol versus Cold Blood Cardioplegia in Patients Undergoing Triple Valve Surgery

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ABSTRACT

Background: The use of Custodiol cardioplegia solution may be tempting in cases undergoing long open-heart surgical procedures, given its single dose administration, which offers myocardial protection for a long period.
Objective: The aim of the current study is to report our initial experience with the use of Custodial cardioplegia in patients undergoing triple valve surgery, and comparing it with our routinely used cold blood cardioplegia.
Patients and Methods: A retrospective observational study including 79 consecutive patients who underwent first-time triple valve surgery in the period between April 2018 and May 2020. Patients were divided into two groups. Group (A) included 31 patients where Custodiol cardioplegia was used, and Group (B) included 48 patients where cold blood cardioplegia was used. The primary endpoint was in-hospital mortality. Secondary endpoints included postoperative levels of CK-Mb, the need for inotropes and the incidence of ventricular fibrillation on aortic declamping.
Results: Apart from a higher incidence of ventricular fibrillation on aortic declamping, there was no statistically significant difference between groups in any of the endpoints examined.
Conclusion: Custodiol cardioplegia is a safe option for myocardial protection in patients undergoing triple valve surgery. The added cost and the concerns about its efficacy in patients with impaired ventricular function reported by other authors should be borne in mind while considering its use.
Keywords: Cardioplegia, Custodiol, Valve surgery.

INTRODUCTION

During open-heart surgery, the adequacy of myocardial protection achieved by cardioplegic solution is one of the major determinants of operative outcomes [(1)]. Over the past decades, various cardioplegic solutions have been tried to optimize myocardial protection during cardiac arrest, with the aim of minimizing myocardial damage hence improving results [(2-5)]. Among those, custom-made blood cardioplegia proved a highly effective alternative [(6)], and continues to be the most commonly used cardioplegic solution in our practice. With a more physiological composition and the added advantage of oxygen carrying capacity, blood cardioplegia has been claimed to be associated with improved outcomes [(7)].

Bretschneider *et al.* initially described Custodiol back in the seventies, as an intracellular crystalloid cardioplegia, with a low sodium and calcium content [(3)]. It is an attractive option for surgeons especially in long surgeries, as it can be administered in a single dose, which is claimed to offer myocardial preservation for up to three hours [(8)]. This allows the performance of long procedures without interruption.

Studies comparing blood cardioplegia to Custodiol often revealed variable results, largely because of the heterogeneity of patient populations studied and the outcome variables reported [(9-11)].

The aim of the current study was to report our initial experience with the use of Custodiol cardioplegia in patients undergoing triple valve surgery, and comparing it to the more commonly used cold blood cardioplegia.

PATIENTS AND METHODS

This retrospective observational study included a total of 79 consecutive patients who underwent first-time triple valve surgery at the Cardiothoracic Surgery Department of Cairo University Hospitals in the period between April 2018 and May 2020.

During this period, a total of 86 patients underwent triple valve surgery involving the mitral, aortic and tricuspid valves. Three patients were excluded due to incomplete files, two patients were excluded due to associated coronary bypass grafting during the surgery and two more patients were excluded on account of redo surgery. The remaining 79 patients were included in the study and their individual files were reviewed to extract clinical, operative and outcome data.

Ethical Consideration:

The study was approved by the local Ethical Committee of Cairo University.

Written consent was obtained from all patients prior to the procedures. This work has been carried out in accordance with the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Study Groups:

Depending on the type of cardioplegia solution used intraoperatively, patients were divided into two groups. Group (A) included 31 patients where Custodiol cardioplegia was used, and Group (B) included 48 patients where cold blood cardioplegia was used.

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Patient's allocation to either group was based on availability of Custodiol cardioplegia solution and surgeon's preference. In group (A) the cardioplegic solution was infused in an antegrade fashion in the aortic root or directly into the coronary ostia in cases of severe aortic regurgitation while in group (B) retrograde delivery of blood cardioplegia was often resorted to. Custodiol was administered after aortic cross-clamping at a temperature of 4-6°C over a period of 6 to 8 minutes. It was to be re-administered only if the aortic cross-clamp time exceeded 120 minutes or in case of earlier detection of electrical activity.

Blood cardioplegia was prepared by mixing oxygenated blood with the home made St Thomas solution at 1:1 ratio. The temperature was lowered to around 4°C. An initial dose of 15 ml/kg was used to induce cardiac arrest after aortic cross-clamping and a maintenance dose of 7 ml/kg was administered every 20 - 30 minutes.

In both groups, myocardial protection involved moderate hypothermic perfusion at around 28°C and topical ice slush.

Outcomes of Interest:

The primary outcome of the study was in-hospital mortality, which was defined as death within the same hospital admission regardless of cause.

Secondary outcomes included the need for inotropes post-bypass, the occurrence of spontaneous ventricular fibrillation (VF) after aortic unclamping, and postoperative CK-Mb levels obtained within the first 24 hours postoperatively.

Statistical Analysis

Data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Comparison of quantitative variables was done using student-*t* test while comparison of categorical data was done using Chi-square test (X^2). A difference was considered significant when $p < 0.05$.

RESULTS

Table 1 outlines the preoperative characteristics of patients, which were comparable except for the body mass index (BMI), which was higher in group (A).

Table (1): Preoperative patient characteristics

	Group (A) N = 31	**Group (B) N = 48**	***P* - value**
Age	34.7 ± 9.3	32.8 ± 10.7	NS
BMI (kg/m^2)	26.4 ± 1.3	22.3 ± 1.5	<0.05
Sex (female)	16 (51.6%)	27 (56.2%)	NS
Diabetes	2 (6.4%)	4 (8.3%)	NS
Hypertension	3 (9.6%)	3 (6.2%)	NS
Current smoker	1 (3.2%)	2 (4.1%)	NS
Serum Creatinine	1.0 ± 0.4	1.1 ± 0.3	NS
Ejection Fraction	54.6 ± 6.1	55 ± 4.9	NS
Atrial Fibrillation	11 (35.4%)	20 (41.6%)	NS
Tricuspid annular plane systolic excursion (TAPSE)	18.5 ± 0.6	18.1 ± 0.5	NS
Pulmonary Pressure (mmHg)	58 ± 9.7	52.6± 12.4	NS
Non-elective procedure	3 (9.6%)	5 (10.4%)	NS

Table 2 shows the operative data. Aortic cross-clamp time and total cardiopulmonary bypass time were comparable in both groups. Given the single administration of Custodiol in group (A) in most cases, retrograde cardioplegia was used more often in group (B).

Table (2): Operative data

	Group (A) N = 31	**Group (B) N = 48**	**P - value**
Procedure: - AVR, MVR + Tricuspid repair - AVR, Mitral and Tricuspid repair	 23 (74.2%) 8 (25.8%)	 38 (79.1%) 10 (20.8%)	NS
Total bypass time	141 ± 39.1	150 ± 31.3	NS
Aortic x-clamp time	109 ± 22.5	116 ± 27.7	NS
Antegrade + Retrograde delivery	2 (6.4%)	21 (43.7%)	<0.05

Table 3 outlines the early postoperative outcomes, which were comparable in both groups, except for a higher incidence of ventricular fibrillation upon release of the aortic clamp in group (A).

Table (3): Postoperative outcomes

	Group (A) N = 31	Group (B) N = 48	P - value
In-hospital Mortality	2 (6.4%)	4 (8.3%)	NS
CK-Mb (Ug/L)	53 ± 9.3	59 ± 11.1	NS
VF on aortic unclamping	13 (41.9%)	12 (25%)	<0.05
Need for Inotropes	25 (80.6%)	38 (79.1%)	NS
Re-exploration for bleeding	3 (9.6%)	4 (8.3%)	NS
Renal Failure requiring dialysis	1 (3.2%)	2 (4.1%)	NS
Deep wound infection	1 (3.2%)	1 (2%)	NS

DISCUSSION

The use of Custodiol cardioplegia in long open-heart surgical procedures such as in triple valve surgeries can be tempting, largely because of its administration in a single initial dose. Avoiding repeat administration of cardioplegia, which is associated with interruption of the surgery and possible trauma from removal and re-application of retractors, would be considered a big advantage by many surgeons. In the current study, we describe our initial experience with Custodiol in such relatively long procedures. Our results show that there was no significant difference in the harder endpoints, between the use of Custodiol and the use of cold blood cardioplegia.

Comparing Custodiol to cold blood cardioplegia in the literature showed variable results. In an experimental setting, **Fannelop *et al.*** [12] reported superiority of multidose blood cardioplegia, with lower troponin-T release in this group and higher cardiac index after declamping. Contrary to that, in their comparative clinical study, **Sakata *et al.*** [9] compared Custodiol to cold blood cardioplegia. They reported more spontaneous defibrillation and less need for inotropes in the Custodiol group. In a randomized study **Braathen *et al.*** [13], showed Custodiol to be as effective as cold blood cardioplegia in mitral surgery, with no significant difference in CK-Mb and troponin-T between Custodiol and blood cardioplegia groups. However, similar to our findings, they reported more ventricular fibrillation in the Custodiol group. In their systematic review comparing Custodiol to conventional cardioplegia, **Edelman *et al.*** [14] included fourteen studies and found no difference in mortality. However, similar to our findings there was an increased incidence of ventricular fibrillation in the Custodiol group, although in their work, this did not attain statistical significance.

Hoyer *et al.* [11] concluded that both Custodiol and cold blood cardioplegia provided equivalent outcomes in a group of patients undergoing isolated aortic valve replacement, although their study showed improved survival in patients with reduced left ventricular ejection fraction (EF less than 30%) when blood cardioplegia was used. Such findings may be related to the distribution rather than the type of cardioplegia used, given the coronary microcirculatory dysfunction that is typically present in patients with aortic stenosis and hypertrophied ventricles [15]. **Gaudino *et al.*** [10], expressed similar concerns, but regarding patients with impaired right ventricular function. In this group of patients, blood cardioplegia offered superior results. We did not note such inferior outcomes in patients with impaired ventricular function. But given the limited number of such patients in our study, such findings should be taken into consideration while contemplating the use of Custodiol.

In our study, the only operative variable that was different between both groups was the more common use of retrograde cardioplegia in group (B). This should have no bearing on the outcomes measured, given the previously documented equivalence of antegrade and retrograde cardioplegia, in terms of postoperative outcomes [16]. The relatively long aortic cross-clamp time in our series was present in many other studies. **Savini *et al.*** [17] showed that there was no significant difference in CK-Mb levels after aortic clamping more than 100 minutes with the use of Custodiol in patients undergoing minimally invasive mitral surgery.

De Haan *et al.* [18], described finding of no difference in early mortality or postoperative levels of CK-Mb in patients requiring prolonged aortic cross-clamp times, when comparing Custodiol to St Thomas cardioplegia.

Hummel *et al.* [19] reported superior outcomes in the Custodiol group compared to blood cardioplegia. The use of Custodiol was associated with less need for blood transfusion and a lesser incidence of stroke and hospital readmission. The cost effectiveness they reported however, would not apply to our clinical practice. In our practice, blood cardioplegia is prepared in house thus not adding any substantial cost, as opposed to the Custodiol solution, which adds a considerable added cost. This is an important point that should be borne in mind, given the relatively limited financial resources in our settings. Also contrary to their findings, apart from a higher incidence of ventricular fibrillation on declamping the aorta, there was no statistically significant difference in any of the other variables examined, including early mortality, postoperative CK-Mb levels, or the need for inotropes.

Limitations of the current study include its retrospective nature, as well the relatively small number of patients reported. However, to the best of our knowledge this is the first study in the English literature to report such a comparison in this specific subgroup of patients. Further studies are needed to examine the role of Custodiol cardioplegia in different subsets of patients.

In conclusion, single dose Custodiol cardioplegia is a safe option for myocardial protection in patients

undergoing triple valve surgery, with an operative mortality and postoperative CK-Mb levels comparable to cold blood cardioplegia. The added cost and the concerns about its efficacy in patients with impaired ventricular function reported by other authors should be borne in mind while considering its use.

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