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TECHNOLOGY REVIEW (MINI-HTA)

CUSTODIOL HTK AS A REPLACEMENT OF BLOOD CARDIOPLEGIA IN CARDIAC SURGERY

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
001/2021

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Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

e-ISBN:978-967-2887-17-1

SUGGESTED CITATION: Syful Azlie MF and Izzuna MMG. Custodiol HTK as a replacement of blood cardioplegia in cardiac surgery. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2021. 33 p. Report No.: 001/2021. e-ISBN: 978-967-2887-17-1

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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EXECUTIVE SUMMARY

Background
Cardioplegic arrest represented one of the most important (probably the greatest) achievement of cardiac surgery in the last 40 years because it allowed, on one hand, the feasibility of treating all heart pathologies with a stopped and bloodless heart and then to ensure, at the same time, myocardial protection during the ischaemic period. Choosing a cardioplegic solution, however, is a significant issue in modern cardiac surgery and it remains controversial as debate continues on the ideal or optimal strategy. A traditional blood cardioplegia is widely used as a method of myocardial protection but it is administered repeatedly every 15 to 30 minutes, which cause interruption of cardiac procedure and therefore are considered a drawbacks of this technique. Recently, there has been growing interest among cardiac surgeons in the use of a more simplified solution that offers simplified perfusion technique, prolonged ischaemic tolerance, and minimised disruption during surgery. Histidine-tryptophan-ketoglutarate (HTK) or Bretschneider's or Custodiol solution has emerged as an option, especially in lengthy cardiac procedures as it is simple to use, administered as one single dose, and it is claimed to give sufficient myocardial protection for more than two hours of cardiac arrest. Hence, this technology review was requested by the Office of the Minister of Health, Malaysia following a proposal from a company to introduce the usage of Custodiol HTK as a replacement for blood cardioplegia in cardiac surgery conducted in MOH hospitals.

Objective/ aim
The objective of this technology review was to identify evidence evaluating the efficacy, safety, and economic implication of Custodiol HTK solution as compared with those obtained using blood cardioplegia in patients undergoing various cardiac surgeries.

Results and conclusions:

Search results
A total of 213 records were identified through the Ovid interface and PubMed while 10 were identified from references of retrieved articles. After reading, appraising and applying the inclusion and exclusion criteria to the 18 full text articles, 12 were included while six were excluded since the studies were already included in systematic review and meta-analysis (n=5) and irrelevant outcome (n=1). Twelve full text articles finally selected for this review comprised of three systematic review and meta-analysis, three randomised controlled trials (RCTs), one retrospective cohort study, two case-controls, one quasi experimental study, and two case series. The studies were conducted mainly in United States, Columbia, United Kingdom, Germany, Italy, Turkey, Greece, Egypt, Saudi Arabia, and Thailand.

Efficacy

There was substantial fair level of retrievable evidence to suggest that a single dose of Custodiol HTK is as effective as repetitive blood cardioplegia in protecting the myocardium in adults and paediatrics cardiac surgery. Both cardioplegia strategies had similar rate for:

i. Myocardial infarction (MI) (2.81% versus 1.62%, risk ratio [RR] 1.72, 95% confidence interval [CI] 0.82 to 3.60; p=0.15).

ii. The release of cardiac enzyme (creatine kinase myocardial band [CK-MB]: mean difference [MD] -4.15, 95 CI -12.41 to 4.10; p=0.32, and troponin-I: MD −1.424 ng/ml, 95% CI −7.747 to 4.898; p=0.659).

iii. Electrocardiographic changes (p=0.176).

iv. Low cardiac output syndrome (LCOS) or inotropes support (risk ratio [RR] 1.3, 95% CI 0.86 to 2.05; p=0.20.

v. Rhythm disturbances (atrial fibrillation [AF] RR 1.36, 95% CI 0.74 to 2.50; p=0.32, and ventricular fibrillation [VF] RR 1.84, 95% CI 0.91 to 3.74; p=0.09).

vi. Blood transfusion or blood product use (57.9% versus 58.9; p=0.514).

vii. Cardiopulmonary bypass (CPB) time (MD 2.103 minutes, 95% CI −2.329 to 6.536; p=0.352).

viii. Aortic cross-clamp time (MD 0.276 minutes, 95% CI −2.569 to 3.120; p=0.849).

However, Custodial HTK compared favourably with blood cardioplegia with regard to:

i. Less severe endothelial injury (postoperative endothelin-1 [ET-1] level, which is among the indicators of systemic endothelial dysfunction has a higher trend and the flow-mediated dilation [FMD] value was lower in blood cardioplegia group; p=0.001 and p=0.043, respectively).

ii. Less incidence of postoperative segmental wall motion abnormalities (SWMA) at postoperative echocardiography (p=0.008).

iii. Shorter mechanical ventilation time (5.97 ± 0.69 versus 9.07 ± 1.27 hours; p<0.001).

Safety

There was substantial fair level of retrievable evidence to suggest that patients receiving Custodiol HTK had a similar risk of mortality as patients receiving blood cardioplegia for myocardial protection in adults (odds ratio [OR] 1.237, 95% CI 0.385 to 3.978; p=0.72) and paediatrics (OR 1.11, 95% CI 0.43 to 2.88; p=0.327). Postoperative complications such as pulmonary, gastrointestinal, reoperation for bleeding, and renal dysfunction or renal failure were comparable between the two strategies.

Organisational

There was substantial fair level of retrievable evidence to suggest that no significant differences were identified between patients receiving Custodiol HTK and blood cardioplegia during cardiovascular surgery in terms of:

i. Length of intensive care unit (ICU) stay (42.8 ± 17.4 hours to 5.43 ± 7.00 days versus 46.4 ± 19.7 hours to 5.39 ± 8.00 days in adults; and MD -0.08, 95% CI -1.52 to 1.36 days for paediatrics in both cardioplegia strategies.

ii. Length of hospital stay (5.48 ± 0.94 days to 10.14 ± 7.67 days versus 5.99 ± 0.91 days to 10.45 ± 7.00 days in adults; and weighted mean difference [WMD] 0.13, 95% CI -0.85 to 1.12 days for paediatrics in both cardioplegia strategies.

iii. Intensive care unit readmission rate (2.4 to 2.8 days versus 3.4 to 5.5 days) in adults.

iv. Hospital readmission rate (5.6 to 14.4 days versus 6.9 to 16.1 days) in adults.

Economic implication

The cost-effectiveness of Custodiol HTK for myocardial protection has not yet been formally evaluated. The first study to look closely at the financial analysis of the solution indicated that there was less hospital readmission within 30 days when using Custodiol HTK cardioplegia which contributed to a significant reduction in patient charge by an average USD 3,103 per patient.

Conclusion

Despite its widespread clinical use, data on the efficacy and safety of Custodiol HTK solution in both adult and paediatric patients undergoing diverse high-risk cardiac surgeries or procedures remain limited. Nevertheless, the retrievable evidence suggests that Custodiol HTK and blood cardioplegia were equivalent in terms of early clinical outcomes for myocardial protection in adult and paediatric populations. Both cardioplegia strategies had similar rate for myocardial infarction (MI) which includes both electrocardiogram-defined and the release of cardiac enzyme (CK-MB, troponin-I, troponin-T, lactate), low cardiac output syndrome (LCOS) defined by the need for inotropic and/or intra-aortic balloon pump support, rhythm disturbances (ventricular fibrillation [VF] as the first rhythm after cross-clamp release and new postoperative atrial fibrillation [AF]), blood transfusion or blood product use, and the duration of cardiopulmonary bypass (CPB) and aortic cross-clamping. In contrast to this, a single dose Custodial HTK compared favourably with traditional repetitive blood cardioplegia with regard to less severe endothelial injury and incidence of postoperative segmental wall motion abnormalities (SWMA), and shorter mechanical ventilation time. Above all, the similar rate of mortality and postoperative complications confirms the safety of the Custodial HTK in comparison to conventional cardioplegia. Lengths of ICU and hospital stay as well as the readmission rate were also comparable between the two strategies. Nonetheless, given the current available evidence with an acceptable safety profile and potential financial benefits, Custodiol HTK could be considered as feasible option and may be used as an effective substitute for blood cardioplegia to enhance myocardial protection in cardiac surgery.

Methods

A systematic review was conducted. Review protocol and search strategy was developed by the main author while literature search was conducted by an *Information Specialist* who searched for published articles related to myocardial protection that comparing Custodiol HTK with conventional cardioplegia (either blood or extracellular crystalloid) in patient undergoing cardiac surgery. The following electronic databases were searched through the Ovid interface: MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) 1946 to Mar 2021. Parallel searches were run in PubMed, US FDA and INAHTA database while additional articles were retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. The last search was conducted on 22nd March 2021.

TABLE OF CONTENTS

ABBREVIATION

AEs	Adverse events or adverse effects
ADMA	Asymmetric dimethylarginine
ATP	Adenosine triphosphate
CPB	Cardiopulmonary bypass
CASP	Critical Appraisal Skills Programme
CABG	Coronary artery bypass grafting
CI	Confidence interval
CK-MB	Creatine kinase myocardial band
ECMO	Extracorporeal membrane oxygenation
ET-1	Endothelin-1
FMD	Flow-mediated dilation
HTK	Histidine-tryptophan-ketoglutarate
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
IABP	Intra-aortic balloon pump
LCOS	Low cardiac output syndrome
LVEF	Left ventricular ejection fraction
MaHTAS	Malaysian Health Technology Assessment Section
MD	Mean difference
MI	Myocardial infarction
MOH	Ministry of Health
NAD	Nicotinamide adenine dinucleotide
NHS	National Health Service
OR	Odds ratio
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Risk ratio
SWMA	Segmental wall motion abnormalities
SMD	Standardized mean difference
US FDA	United States Food and Drug Administration
VF	Ventricular fibrillation
vWF	von Willebrand factor
WMD	Weighted mean difference

1.0 BACKGROUND

Myocardial ischaemia reperfusion is defined as myocardial damage resulting from the restoration of blood flow to ischaemic tissue. Ischaemia causes a pattern of metabolic responses that result in a reduction of cellular adenosine triphosphate (ATP), a transition from aerobic to anaerobic energy utilization, and an accumulation and secretion of anaerobic metabolic products. Reperfusion can produce an array of events such as damage to cellular and organelle membranes, oxidative stress, endothelial damage and vasoconstriction, and cellular and non-cellular pro-inflammatory immune responses. In the context of cardiac surgery, myocardial protection refers to the strategies and techniques used during the operation to prevent ischaemia reperfusion injury. These strategies help lower the heart metabolic demands, minimizing myocardial stunning and perioperative necrosis or myocardial infarction (MI). Despite the importance of myocardial protection, controversies remain regarding the most clinically effective method to prevent ischaemia reperfusion.[1-2]

One strategy for myocardial protection is the use of cardioplegia, administered at the time of myocardial arrest. Cardioplegic solutions lower the metabolic demand of the heart and protect the myocardium by preserving metabolic substrates, as well as avoiding osmotic, electrolytic, and pH imbalances.[3] The cardioplegic solutions currently used can be classified into two main groups according to their electrolytic composition. One is based on extracellular components with high potassium, magnesium and bicarbonate levels, while the other is based on intracellular electrolytes. Blood cardioplegia, an extracellular cardioplegia remains the preferred strategy for myocardial protection based on the fact that blood as compared with crystalloid solutions can improve postoperative outcomes due to its structure being closer to the normal physiology. However, this technique must be administered repeatedly every 15-30 minutes to maintain its protective properties, which causes interruption during cardiac procedure.[4-5] Histidine-tryptophan-ketoglutarate (HTK) or Bretschneider's or Custodiol solution is an example of intracellular cardioplegia characterized by low sodium and calcium contents. In many countries, it has been used not only as a cardioplegic agent but also as multiorgan-preserving solutions in transplant surgery.[6] Unlike standard blood cardioplegia, Custodiol HTK is generating considerable interest among cardiac surgeons as it is simple to use, administered as one single dose, and it is claimed to give sufficient myocardial protection for more than two hours of cardiac arrest (minimizes disruption to the technical flow of the operation).[7]

Despite its widespread use, there is very little data comparing the effects of Custodiol HTK against other common forms of cardioplegic solution. Hence, this technology review was requested by the Office of the Minister of Health, Malaysia following a proposal from a company to introduce the usage of Custodiol HTK as a replacement for blood cardioplegia in cardiac surgery conducted in MOH hospitals.

2.0 OBJECTIVE / AIM

The objective of this technology review was to identify evidence evaluating the efficacy, safety, and economic implication of Custodiol HTK solution as compared with those obtained using blood cardioplegia in patients undergoing various cardiac surgeries.

3.0 TECHNICAL FEATURE

In general, blood-based or crystalloid-based solutions are used as potassium-containing transport medium. Blood cardioplegia is mixed in a ratio of 1:4 (1 part of crystalloid solution and 4 parts of blood); crystalloid solutions may be of intracellular type (Custodiol) or extracellular type (Plegisol). Specific details are given in **Table 1**.[4-5]

Table 1: Composition of crystalloid (intracellular type: Custodiol, HTK, Bretschneider's, and extracellular type: Plegisol, St. Thomas solution) and blood-based cardioplegic solutions

	Crystalloid-based cardioplegia		Blood-based cardioplegia		
Formulation ingredient	Intracellular Custodiol, HTK, Bretschneider's	Extracellular Plegisol, St. Thomas solution	Blood cardioplegia induction 4:1	Blood cardioplegia maintenance 4:1	Units
Na^+	15	110	140	140	mmol/L
K^+	9	16	20	10	mmol/L
Mg^{2+}	4	16	13	9	mmol/L
Ca^{2+}	0.015	1.2	-	-	mmol/L
Histidine	198	-	-	-	mmol/L
Tryptophan-	2	-	-	-	mmol/L
Ketoglutarate	1	-	-	-	mmol/L
Mannitol	30	-	-	-	mmol/L
Glucose	-	-	6	6	mmol/L
Lidocaine	-	-	260	-	mg/L
pH	7.02-7.20	7.80	7.20	7.40	$[H^+]$

Figure 1: Custodial HTK solution

WHAT IS A CUSTODIOL HTK?

The purpose of cardioplegia is to produce myocardial arrest in the diastolic phase of the cardiac cycle, to decrease metabolism and to support normal physiology during ischaemia. In this regard, Custodiol HTK is an appealing cardioplegic agent for minimally invasive cardiac surgery. It is given as one dose and offers myocardial protection for up to two hours, thus allowing uninterrupted operation.[8] It is an intracellular crystalloid cardioplegic agent with low concentrations of sodium and calcium. The washout of extracellular sodium causes hyperpolarisation of the myocyte plasma membrane and induces a diastolic cardiac arrest while permeability is reduced and protons are equilibrated in the extracellular space.[9] Histidine, which is a high-capacity buffer of acidic anaerobic metabolites, migrates inside the cell and balances the ischaemic intracellular accumulation of hydrogen ions and lactate. It also enhances the efficiency of anaerobic glycolysis. Tryptophan on the other hand stabilizes the cell membrane. Ketoglutarate, an intermediary in the Kreb cycle (nicotinamide adenine dinucleotide [NAD] precursor), assists in ATP regeneration during reperfusion. In addition, mannitol component decreases cellular oedema and acts as a free radical scavenger.[10]

Custodiol HTK has also been used frequently for organ preservation in solid organ transplant with long-standing ischaemia since the United States Food and Drug Administration (US FDA) approved it for perfusion and flushing of donor kidneys, liver, pancreas and heart prior to removal from the donor or immediately after removal from the donor.[6, 11]

4.0 METHODS

A systematic review was conducted. Review protocol and search strategy was developed by the main author and *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface: **MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) 1946 to Mar 2021.**

Other databases:

- PubMed
- Other websites: US FDA, INAHTA.

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 22nd March 2021.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist* and Cochrane risk of bias tool for randomised trials (RoB 2). Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). Data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Patients (adult and paediatric) undergoing cardiovascular surgery requiring cardioplegic arrest
b.	**Intervention**	Custodiol HTK solution, histidine-tryptophan-ketoglutarate solution, Bretschneider's solution, crystalloid cardioplegia, intracellular cardioplegia solution
c.	**Comparator**	Blood cardioplegia, extracellular cardioplegia solution
d.	**Outcomes**	**Efficacy:** Myocardial protection: *myocardial infarction (MI), cardiac enzyme release, low cardiac output syndrome (LCOS) or use of inotropes/ intra-aortic balloon pump (IABP) support, rhythm disturbances, spontaneous defibrillation, aortic cross-clamp time, cardiopulmonary bypass (CBP) time, mechanical ventilation time* **Safety:** *Mortality or operative death, adverse events (AEs), postoperative complications* **Organisational issues:** *Hospital utilisation (readmission, length of stay), procedural time points and training or learning curve* **Economic implications:** *Cost, cost-effectiveness, cost-utility analysis*
e.	**Study design**	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, case-control, case series, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case report, animal study, laboratory study, narrative review
b.	Non English full text articles	

5.0 RESULTS

Search results

An overview of the search is illustrated in **Figure 2**. A total of **213** records were identified through the Ovid interface and PubMed while **10** were identified from references of retrieved articles. No duplicates references were found; **223** potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, **18** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **18** full text articles, **12** were included while **six** were excluded since the studies were already included in systematic review and meta-analysis (n=5) and irrelevant outcome (n=1). Twelve full text articles finally selected for this review comprised of three systematic review and meta-analysis, three RCTs, one retrospective cohort study, two case-controls, one quasi experimental study, and two case series. The studies were conducted mainly in United States, Columbia, United Kingdom, Germany, Italy, Turkey, Greece, Egypt, Saudi Arabia, and Thailand.

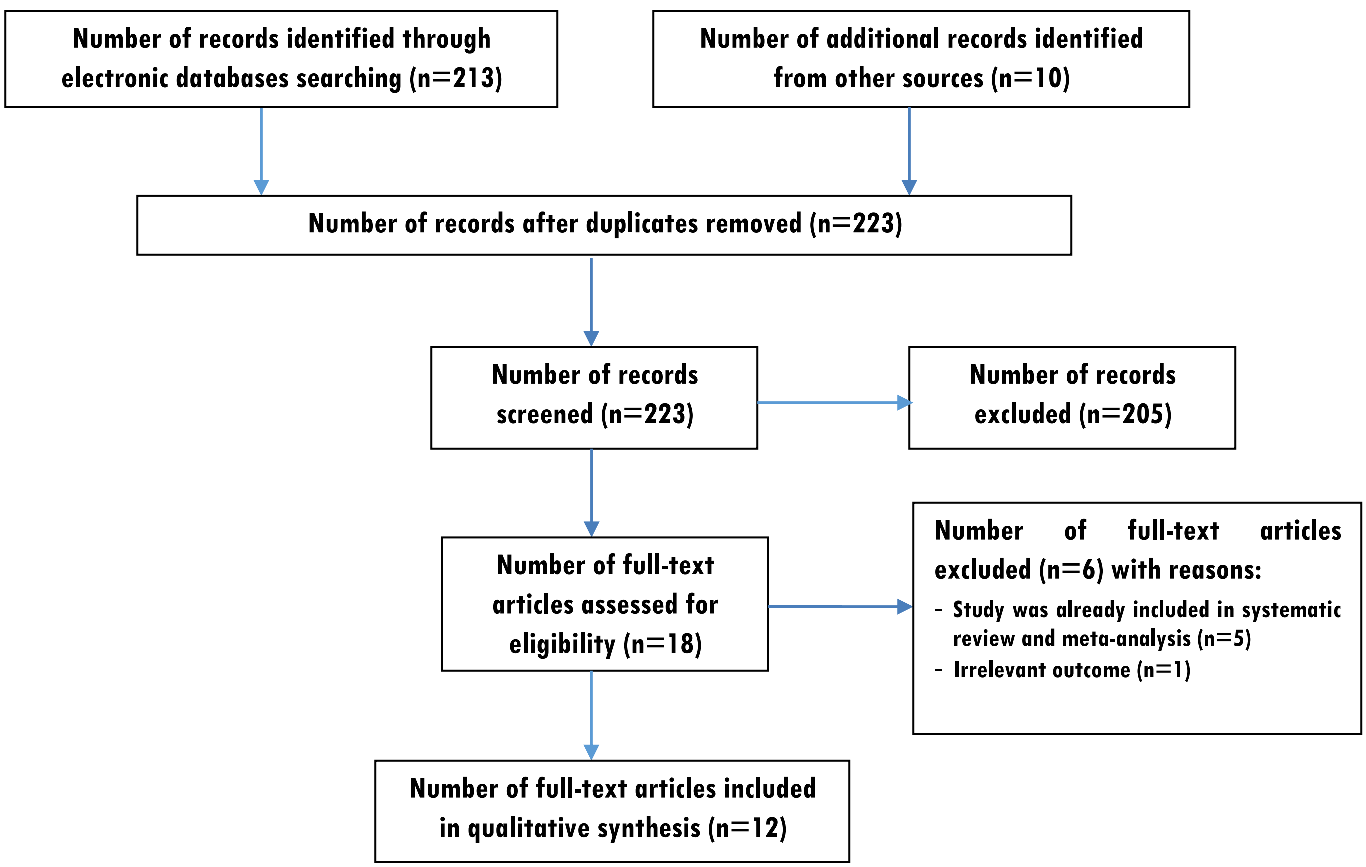

Figure 2: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias in the included studies were assessed using domain-based evaluation. Tools that are being used by MaHTAS to assess the risk of bias are adapted from the CASP checklist whereas Cochrane risk of bias tool (RoB 2) was used for randomised trials. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

Overall, the risk of bias were low for systematic review except for assessment quality of included studies which was not reported in one study (Edelman JJ 2013). For RCTs, no random element was used in generating the allocation sequence in two studies (Mercan I 2020 and Hamed MA 2018) while study by Hamed MA 2018 revealed that outcome assessors were aware of the intervention received by study participants. In contrast to this, low risk of bias were observed for cohort, case-control, and quasi experimental study. The results of risk of bias of included studies are summarised in **Figure 3.1 and 3.5**

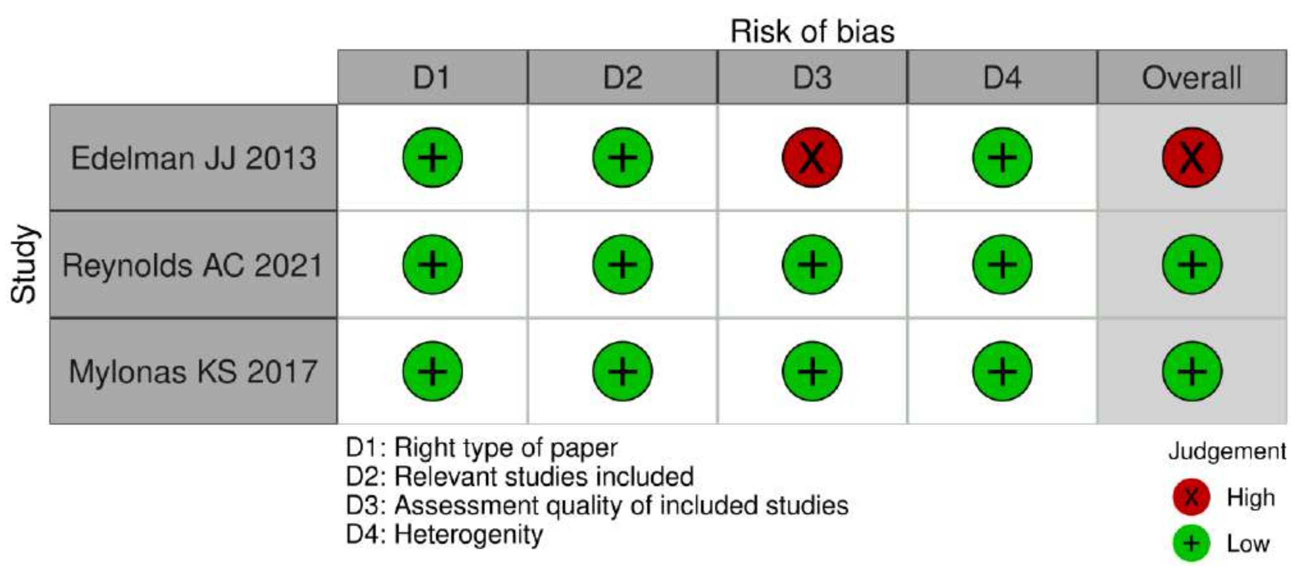

Figure 3.1: Assessment of risk of bias of systematic review (CASP)

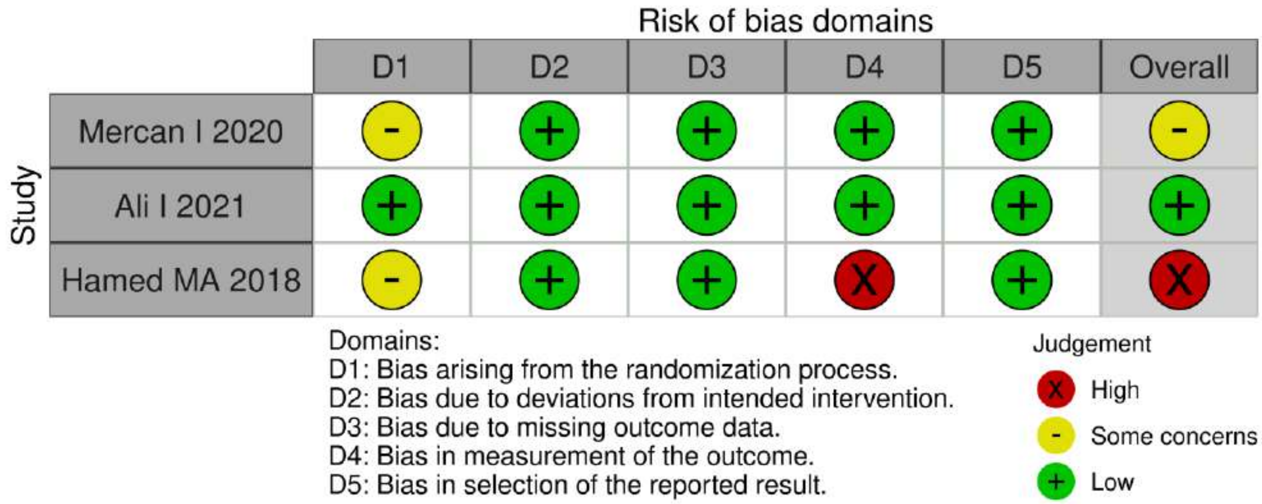

Figure 3.2: Assessment of risk of bias of RCT (RoB 2)

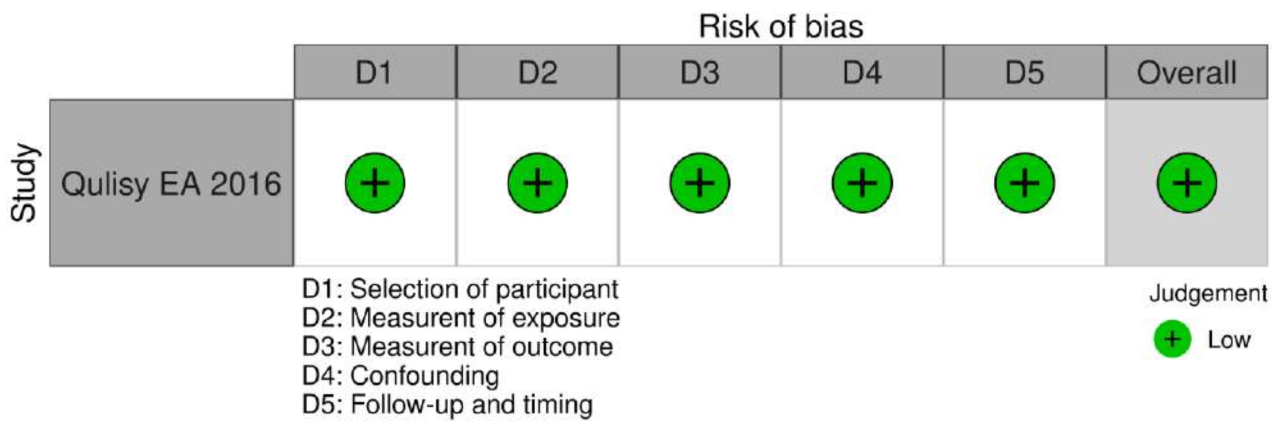

Figure 3.3: Assessment of risk of bias of cohort study (CASP)

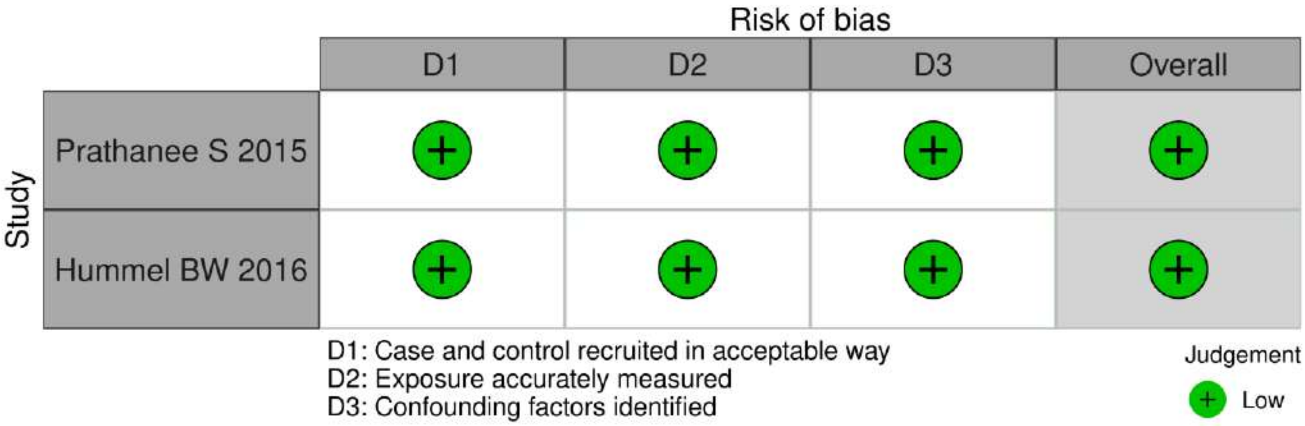

Figure 3.4: Assessment of risk of bias of case-control (CASP)

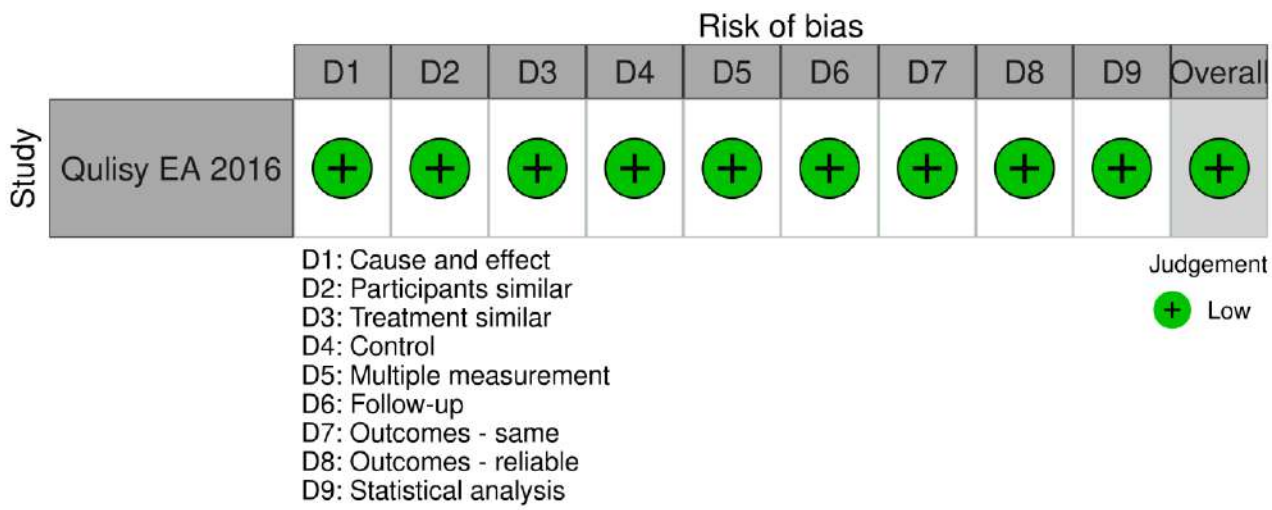

Figure 3.5: Assessment of risk of bias of quasi experimental study (JBI)

5.1 EFFICACY

POPULATION: ADULTS

In 2013, Edelman JJ et al. performed a meta-analysis (14 studies; n=2,114) comparing Custodiol HTK with conventional cardioplegia (blood or extracellular crystalloid) in adult patients undergoing cardiac surgery. The analysis suggested no significant difference between Custodiol HTK and conventional cardioplegia, particularly for the rate of MI (Custodiol HTK 2.81% versus conventional 1.62%, risk ratio [RR] 1.72, 95% CI 0.82 to 3.60; p=0.15), the release of cardiac enzyme (creatine kinase myocardial band [CK-MB]: mean difference [MD] -4.15, 95% CI -12.41 to 4.10; p=0.32; troponin-I: MD 0.90, 95% CI -4.68 to 6.48; p=0.75), cross-clamp time (weighted mean: Custodiol HTK 62.9 minutes versus conventional 54.8 minutes; p=0.11), and the rate of inotropes/ LCOS (Custodiol HTK 15.0% versus conventional 12.7%, RR 1.3, 95% CI 0.86 to 2.05; p=0.20). Indeed, there was a trend for increased incidence of ventricular arrhythmias during reperfusion that reached statistical significance in the fixed but not the random effects model (Custodiol HTK 20.1% versus 9.7%, random effects: RR 1.84, 95% CI 0.91 to 3.74; p=0.09; fixed effects: RR 2.12, 95% CI 1.63 to 2.76; p<0.001). There was also no significant difference in the rate of AF between groups (Custodiol HTK 34.3% versus conventional 17.7%, RR 1.36, 95% CI 0.74 to 2.50; p=0.32).[12, level II-2]

The most recent meta-analysis by Reynolds AC et al. (2021) identified seven RCTs involving 804 participants with either coronary artery disease or valvular disease; 412 of whom were Custodiol HTK patients versus 391 who received multidose cardioplegias (blood or extracellular crystalloid). The primary outcomes analysed were cardiopulmonary bypass (CPB) time, aortic cross-clamp time, spontaneous defibrillation (spontaneous return of heartbeat), inotropic support, AF, CK-MB, and troponin-I. The study showed that spontaneous defibrillation following aortic cross-clamp removal significantly favoured Custodiol HTK (odds ratio [OR] 2.809, 95% CI 1.574 to 5.012; p<0.01). However, there were no other notable significant differences between two groups in any of the parameters measured: CPB time (MD 2.103 minutes, 95% CI −2.329 to 6.536; p=0.352), aortic cross-clamp time (MD 0.276 minutes, 95% CI −2.569 to 3.120; p=0.849), inotropic support (OR 1.5, 95% CI 0.742 to 3.032; p=0.259), AF (OR 0.809, 95% CI 0.511 to 1.281; p=0.366), and the release of CK-MB (standardized mean difference [SMD] −0.046, 95% CI −0.27 to 0.178; p=0.687) and troponin-I (MD −1.424 ng/ml, 95% CI −7.747 to 4.898; p=0.659).[13, level I]

Mercan I et al. (2020) conducted an RCT to determine the effects of Bretschneider's HTK solution and cold blood cardioplegia on systemic endothelial function. A total of 50 patients with no gender preference that are between 40 and 80 years were included. The patients in whom an isolated coronary artery bypass grafting (CABG) were randomly divided into two groups: Bretschneider's HTK solution (n=25) and cold blood cardioplegia (n=25). Data related to the indicators of systemic endothelial dysfunction were recorded. Flow-mediated dilation

(FMD) was measured together with the assessment of the values of endothelin-1 (ET-1), von Willebrand factor (vWF), lactate, and asymmetric dimethylarginine (ADMA). The two groups were then compared regarding these values. All data except FMD were recorded preoperatively (T0), and at day 0 (T1), day 1 (T2), day 3 (T3), and day 5 (T4) during the postoperative period. The study revealed that Bretschneider's HTK solution causes less severe endothelial injury than cold blood cardioplegia. While ADMA (p=0.115), vWF (p=0.892), and lactate (p=0.202) levels were found to be similar, the postoperative ET-1 level was determined to be higher, and the FMD value was significantly lower in blood cardioplegia group (p=0.001 and p=0.043, respectively). When the two study groups were compared regarding the medical data, no statistical differences were found in terms of aortic clamping time, duration of CPB and cross-clamping, and intraoperative blood product use. Spontaneous heartbeat, however, was significantly higher in the blood cardioplegia group (p=0.024).[14, level I]

Recently, Ali I et al. (2021) compared the efficacy between the Custodiol HTK solution and blood cardioplegia in 320 patients (aged 30-70 years old) undergoing various cardiac surgeries. Randomisation was done by a statistician who was not involved in the study while opaque sealed envelopes were prepared and opened by a clinician not involved in any part of the study. Cardiac enzyme levels (troponin >20 mg/l, CK-MB >30 U/l) 12 and 24 hours postoperatively, segmental wall motion abnormalities (SWMAs), and at least two new Q waves on two consecutive electrocardiograms and pericardial effusion, electrocardiographic changes such as ventricular fibrillations or ventricular arrhythmia, cross-clamp and total bypass time, requirement for inotropic support, and intra-aortic balloon use were analysed. The result of this RCT revealed that the administration of Custodiol HTK solution as a single initial dose for patients undergoing cardiac surgeries was associated with shorter cross-clamp and total bypass time, and the duration of mechanical ventilation (all p<0.001). It was also associated with lower number of patients requiring inotropic support (p<0.001) and less incidence of postoperative SWMA (p=0.008). In contrast to this, preoperative and postoperative ejection fractions were comparable (p=0.380 and p=0.885, respectively) while the incidence of pericardial effusion and electrocardiographic were similar between the two study groups (p=0.090).[15, level I]

A retrospective case-control study in 125 patients who underwent triple vessels coronary artery disease and had performed CABG were reviewed in Cardiovascular and Thoracic Unit, Department of Surgery, Khon Kaen University, Thailand during April 2011 and September 2012. They were divided into two groups for myocardial protection by blood cardioplegia (n=60) and Custodiol HTK (n=65). Primary outcome of this study was ventricular fibrillation (VF) after removal of aortic cross clamp, which occurred more frequently in Custodiol HTK group (33.8% versus 8.3%; p=0.001). Cardiopulmonary bypass and aortic cross clamp time were significantly longer in the blood cardioplegia compared to the Custodiol HTK group (p=0.027 and p=0.046, respectively).[16, level II-2]

In a single-institution case-control study by Hummel BW et al. (2016), the authors retrospectively analysed 362 matched patient in order to avoid as much as possible selection biases; 181 valve cases (aortic or mitral) performed using Custodiol HTK were compared with 181 cases performed with traditional blood cardioplegia. The study indicated that a single-dose Custodiol HTK was as effective as repetitive cold blood cardioplegia in protecting myocardium. Patients had similar outcomes including postoperative AF occurrence, prolonged ventilation, and postoperative peak troponin-I. The Custodiol HTK group, however, had statistically significant improvement in blood transfusion (p<0.03).[17, level II-2]

Savini C et al. (2014) reported early outcomes of 49 consecutive patients underwent minimally invasive mitral valve surgery using a single dose of Custodiol HTK solution for myocardial protection. It is evident from the data that showed the mean CPB time was 148.6 ± 45.0 minutes, aortic cross-clamp duration 97.9 ± 45.0 minutes, and assisted ventilation time 9.3 ± 15.9 hours. The heart after removal of the cross-clamp restarted spontaneously in 37 cases (75.5%), and ventricular arrhythmias requiring electrical cardioversion to sinus rhythm occurred in the remaining 12 cases (24.5%). The incidence of AF in the postoperative period occurred in 12 patients (24.5%). No significant modifications in myocardial cytonecrosis enzymes were found at three, 12, and 24 hours after surgery regardless of cross-clamp time duration (>100 or <100 minutes). Consistently, no ischaemic electrocardiogram modifications were observed before discharge. None of the patients developed LCOS postoperatively, and only five patients (10.2%) needed mild-to-moderate postoperative inotropic support.[18, level II-2]

In a non-randomised single centre experimental study by Pizano A et al. (2018), they compared intraoperative and postoperative effects of Custodiol HTK solution with those of standard blood cardioplegia. The study was conducted using a large cohort of adult cardiac patients undergoing diverse surgical procedures. Patients were divided into a HTK solution group (n=628) and blood cardioplegia group (n=3,852). Propensity score matching was used to adjust for differences between the two groups (to reduce confounding bias); 292 matched pairs were identified and included in the study. No significant differences were found between the matched groups with regard to demographic characteristics or type of procedures performed. Regarding intraoperative variables, the HTK group had shorter aortic cross-clamp times (98.5 ± 39 minutes versus 116.1 ± 38 minutes; p<0.001) and shorter CPB times (132.8 ± 53 minutes versus 147 ± 47 minutes; p=0.001). Following cardioplegia delivery, patients in the HTK group showed a significant decrease in serum sodium concentration during CPB compared to patients who received blood cardioplegia. The serum sodium concentration returned to normal values on the first postoperative day. In the HTK solution group, 87 (29.8%) patients required a second dose of cardioplegia due to return of electrical activity. No patients required a third dose of HTK solution. Furthermore, no significant differences was found in blood product usage.[19, level II-2]

POPULATION: PAEDIATRICS

Paediatric patients are at high risk of cardiac ischaemic injury which is due to reduce free radical scavenging, increase sensitivity to calcium, and unknown factors related to the unique environment of the cyanotic heart. Meanwhile, the immature heart's unique physiology including the preference for glucose as a substrate, large stores of glycogen and the low activity of 5-nucleotidase, could provide some protection against ischaemic damage. Together with therapeutic hypothermia, cardioplegia can supplement metabolic substrate and decrease cardiac oxygen consumption.[20] When congenital cardiac surgery was first introduced, cardioplegia was essentially the same to the one used for adults and was simply adjusted for volume, flow, and pressure.[21] However, there is scarce data regarding its use in infants and children. There is an ongoing discussion about the relative effectiveness of these solutions considering myocardial protection.

Mylonas KS et al. (2017) performed a systematic review of the literature for all original studies on the use of blood versus crystalloid cardioplegia. In total, 7,711 paediatric patients (56 studies) underwent cardiac surgery using either blood (n=6,289) or crystalloid cardioplegia (n=1,422) over a 40-year period (1973–2014). A meta-analysis of the 10 eligible studies directly comparing blood (n=416) to crystalloid cardioplegia (n=281) demonstrated no significant difference between the two groups with regard to cardiac troponin-I and lactate levels at any measured time point, ATP levels after reperfusion, aortic cross-clamp time, CPB time, circulatory arrest time, mechanical ventilation time, and postoperative need for extracorporeal membrane oxygenation (ECMO) or significant inotropic support. In contrast to this, only cardiac troponin-I levels at 4-hour postoperatively were significantly lower in the blood cardioplegia group (WMD -1.62 ng/ml, 95% CI -2.07 to -1.18) while ATP-pre levels were significantly higher in the crystalloid cardioplegia group (WMD -6.44 nmol/mg, 95% CI -8.33 to -4.55).[22, level II-2]

A prospective randomised controlled double blinded clinical study by Hamed MA and Abdel-Ghaffar RA (2018) compared the myocardial protective effects of three types of cardioplegia solution among 60 children (aged 3-10 years of either sex) who underwent elective cardiac surgery for acyanotic heart diseases using CPB at Cairo National Heart Institute from June 2015 to October 2017. Patients were randomly allocated to three groups solutions (each one 20); Group A received Custodiol HTK cardioplegia. Group B received blood cardioplegia, and Group C received St. Thomas cardioplegia. Regarding duration of CPB, aortic cross-clamp time, and the whole surgical duration, the results were similar between the study groups (p>0.05). Troponin-T levels recorded at six and 12 hours after the operation were not statistically significant difference except that recorded 24 hours; the highest level was in the group B (28.1 ± 2.4 ng/ml) and the lowest in group C (24.5 ± 3 ng/ml). The CK-MB levels was also not statistically significant different among the study groups except that recorded after 12 hours; the highest was in group C (147.8 ± 28.1 ng/ml) and the lowest in group B (128.2 ± 24. ng/ml 6). On the other hand, there were statistically significant differences (p=0.001) for extubation and mechanical ventilation time, with the longest time was in the group B and the shortest in the group A. There were 1.5 ± 0.4 hours and 5.2 ± 0.8 hours in group A; 5.1 ± 0.6 hours and 8.5 ± 1.1 hours in group B; and 3.3 ± 1.2 hours and 6.9 ± 1.8 hours in group C. There was also statistically significant difference between the study groups regarding the use of inotropic support with highest percentage (100%) of use in group A, followed by 90% for group C and lowest percentage for group B (65%).[23, level II-1]

Qulisy EA et al. (2016) reported the outcomes between Custodiol HTK and cold blood cardioplegia by carrying out a multi-centred, retrospective cohort study between November 2013 and June 2014. A total of 154 children (1 day to 18 years of age) who underwent congenital heart surgery with the use of CPB were identified from a prospective database and additional data were collected from operative report and electronic and paper charts. Patients were then divided into two groups on the basis of the cardioplegia solution used (Custodiol HTK was administered in 66 patients; 88 in blood cardioplegia). A composite endpoint of all cause death, LCOS, acute kidney injury, and significant arrhythmia was analysed with a multiple logistic regression model adjusted for complexity using the Risk Adjustment of Congenital Heart Surgery-1 (RACHS-1) categories. The study indicated that children including neonates who receive Custodiol HTK for myocardial protection may be associated with less effective myocardial protection and higher adverse outcomes compared to blood cardioplegia. In an unadjusted outcomes, patients receiving Custodiol HTK had longer mechanical ventilation times compared to blood cardioplegia (median 72 versus 47 minutes; p=0.005). A trend was also noted for more prevalent LCOS (33% versus 23%; p=0.14). Whereas in the risk adjusted comparison of the composite outcome, Custodiol HTK cardioplegia was found to be an independent predictor of an adverse outcome (OR 3.17, 95% CI 1.41 to 7.14; p=0.0054).[24, level II-2]

In a recent single-centre retrospective review by Bibevski S et al. (2020), echocardiographic data of 133 patients (<12 months old) undergoing biventricular repair were compared between the two groups who received single-dose Custodiol HTK (n=106) and multi-dose blood cardioplegia (n=27). Results showed that the average CPB time was similar between both groups (Custodiol 93 ± 54 minutes versus blood 81 ± 44 minutes; p=0.46) as was aortic cross-clamp time (Custodiol 58 ± 33 minutes versus cold blood 53 ± 33 minutes; p=0.62). Preoperative left ventricular ejection fraction (LVEF) was similar between Custodiol and blood (70 ± 9% versus 73 ± 8%; p=0.21). There was also no intergroup difference in LVEF 24 hours postoperative (Custodiol 65 ± 12% versus blood 64 ± 9%; p=0.53) or at discharge (Custodiol 66 ± 11% versus blood 66 ± 10%; p=0.95). The preoperative right ventricle function by fractional area change was also similar in Custodiol (48 ± 9%) versus blood cardioplegia (46 ± 13%; p=0.38) and showed similar drops in parameters in the two groups 24 hours after surgery and at discharge.[25, level II-2]

Summary of studies related to efficacy of Custodial HTK versus blood cardioplegia are shown in **Table 2 (adults)** and **Table 3 (paediatrics)**.

Table 2: Efficacy of Custodial HTK versus blood cardioplegia in adults reported by the included studies

Myocardial protection indicators	Authors/ study design							
	Edelman JJ 2013 (SR&MA)	Reynolds AC 2021 (SR&MA)	Mercan I 2020 (RCT)	Ali I 2021 (RCT)	Prathanee S 2015 (case-control)	Hummel BW 2016 (case-control)	Savini C 2014 (case-series)	Pizano A 2018 (quasi-experimental)
Rate of MI	Not significant difference	-	-	-	-	-	0.0%	-
Release of CE (CK-MB, troponin-I)	Not significant difference	Not significant difference	-	Not significant difference	-	Not significant difference	CK-MB 38.4%	-
ECG changes (LVEF, RVEF)	-	-	-	Not significant difference	-	-	LVEF 61.2%	-
Rate of inotropes/ LCOS	Not significant difference	Not significant difference	-	Lower in Custodiol HTK	-	-	10.2%	-
CPB time	-	Not significant difference	Not significant difference	Shorter in Custodiol HTK	Shorter in Custodiol HTK	-	148.6 min	Shorter in Custodiol HTK
Cross-clamp time	Not significant difference	Not significant difference	Not significant difference	Shorter in Custodiol HTK	Shorter in Custodiol HTK	-	97.9 min	Shorter in Custodiol HTK
MV time	-	-	-	Shorter in Custodiol HTK	-	-	-	-
Rate of VF	Not significant difference	-	-	-	Increase in Custodiol HTK	-	-	-
Rate of AF	Not significant difference	Not significant difference	-	-	-	Not significant difference	24.5%	-
Blood product use/ blood transfusion	-	-	Not significant difference	-	-	Lower in Custodiol HTK	0.35%	Not significant difference

SR&MA, systematic review & meta-analysis; RCT, randomised controlled trial; MI, myocardial infarction; CE, cardiac enzyme; CK-MB, creatine kinase myocardial band; CPB, cardiopulmonary bypass; MV, mechanical ventilation; LCOS, low cardiac output syndrome; AF, atrial fibrillation; VF, ventricular fibrillation; ECG, electrocardiogram; LVEF; left ventricular ejection fraction; RVEF, right ventricular ejection fraction

Table 3: Efficacy of Custodial HTK versus blood cardioplegia in paediatrics reported by the included studies

Myocardial protection indicators	Authors/ study design			
	Mylonas KS 2017 (SR&MA)	Hamed MA 2018 (RCT)	Qulisy EA 2016 (cohort)	Bibevski S 2020 (case-series)
Release of CE (troponin-I, troponin-T, lactate)	Not significant difference	Not significant difference	-	-
Cardiopulmonary bypass time	Not significant difference	Not significant difference	Not significant difference	Not significant difference
Cross-clamp time	Not significant difference	Not significant difference	Not significant difference	Not significant difference
Mechanical ventilation time	Not significant difference	Shorter in Custodiol HTK	-	-
Extubation time	-	Shorter in Custodiol HTK	-	-
Rate of inotropes/ LCOS	Not significant difference	Higher in Custodiol HTK	Higher in Custodiol HTK	-
ECG changes (LVEF, RVEF)	-	-	-	Not significant difference
ATP level after reperfusion	Not significant difference	-	-	-
Need for ECMO	Not significant difference	-	-	-

SR&MA, systematic review & meta-analysis; RCT, randomised controlled trial; CE, cardiac enzyme; CPB, cardiopulmonary bypass; LCOS, low cardiac output syndrome; ECG, electrocardiogram; LVEF; left ventricular ejection fraction; RVEF, right ventricular ejection fraction; ATP, adenosine triphosphate; ECMO, extracorporeal membrane oxygenation

5.2 SAFETY

Overall, patients receiving Custodiol HTK had a similar risk of mortality as patients receiving blood cardioplegia for myocardial protection, both in adult [12-13, 15-17, 19] and paediatric populations.[22, 24-25] In a meta-analysis that included 14 studies comprising 2,114 patients undergoing cardiac surgery, the rate of mortality was 2.70% in the Custodiol group as compared with 2.63% in the blood group (RR 1.05, 95% CI 0.59 to 1.88; p=0.86).[12, level II-2] The same results were confirmed by a more recent meta-analysis of seven RCTs with an OR of 1.237 (95% CI 0.385 to 3.978; p=0.721).[13, level I] Mortality was not observed in any of the patients included in two studies[14, level I and 18, level II-2] while one did not reported.[23, level II-1]

Similarly, postoperative complications were comparable between the two strategies in the rate of pulmonary (postoperative atelectasis, exacerbation of chronic obstructive pulmonary disease, pulmonary oedema) and gastrointestinal complications (dyspepsia), neurologic events, acute renal dysfunction or renal failure (needed dialysis or temporary urea and creatinine elevation), new heart failure, reoperation for bleeding, antibiotic revision, temporary arrhythmia, and other major postoperative complications including clinical stroke and deep sternal wound infection or post-operative intra-aortic balloon pump implantation.[14-22, 24]

5.3 ORGANISATIONAL ISSUES

In the context of a limited prognosis, avoiding intensive care unit (ICU) or hospital stays may be an important consideration for patients. This includes not only days related to the procedure itself, but also subsequent stays caused by recurrences or complications. Following this, most findings reported no significant difference for both adults and paediatrics patients undergoing cardiovascular surgery requiring cardioplegic arrest, although lengths of ICU and hospital stay were shorter in the Custodiol HTK than in the blood cardioplegia.[14, 16, 19, 22, 24] Given this information, two studies indicated a significant reduction or shortened lengths of ICU (range from 17.1 ± 0.3 hours to 2.05 ± 0.22 days versus 58.8 ± 10.9 hours to 2.14 ± 0.35 days; p<0.001) and hospital stay (range from 5.48 ± 0.94 versus 5.99 ± 0.91 days; p<0.001).[15, level I and 23, level II-1]

More generally, three studies reported a similar rate between the two methods with regard to ICU [17, 19] and 30-day hospital readmission.[15, 19] However, in a retrospective case-control series of patients having valve surgery, the Custodiol HTK cardioplegia group had a statistically significant improvement in hospital readmission within 30 days (6.1% versus 13.8%; p<0.05).[17, level II-2]

Summary of studies related to organisational issues of Custodial HTK versus blood cardioplegia are shown in **Table 4.**

Table 4: Organisational issues of Custodial HTK versus blood cardioplegia reported by the included studies

Authors/ study design	Length of stay (day)				Readmission rate (%)			
	ICU		Hospital		ICU		Hospital	
	Custodiol HTK	Blood cardioplegia	Custodiol HTK	Blood cardioplegia	Custodiol HTK	Blood cardioplegia	Custodiol HTK	Blood cardioplegia
ADULTS								
Edelman JJ 2013 (SR&MA)	-	-	-	-	-	-	-	-
Reynolds AC 2021 (SR&MA)	-	-	-	-	-	-	-	-
Mercan I 2020 (RCT)	42.8 ± 17.4 hrs	46.4 ± 19.7 hrs	-	-	-	-	-	-
Ali I 2021 (RCT)	**2.05 ± 0.22**	**2.14 ± 0.35**	**5.48 ±0.94**	**5.99 ± 0.91**	-	-	5.6	6.9
Prathanee S 2015 (case-control)	2.25 ± 1.72	1.98 ± 1.98	10.14 ± 7.67	10.45 ± 7.00	-	-	-	-
Hummel BW 2016 (case-control)	-	-	-	-	2.8	5.5	**6.1**	**13.8**
Savini C 2014 (case-series)	1.69 ± 1.44	-	-	-	-	-	-	-
Pizano A 2018 (quasi-experimental)	5.43 ± 7.00	5.39 ± 8.00	-	-	2.4	3.4	14.4	16.1
PAEDIATRICS								
Mylonas KS 2017 (SR&MA)	WMD -0.08, 95% CI -1.52 to 1.36		WMD 0.13, 95% CI -0.85 to 1.12		-	-	-	-
Hamed MA 2018 (RCT)	**17.1 ± 0.3**	**58.8 ± 10.9**	-	-	-	-	-	-
Qulisy EA 2016 (cohort)	7 (3, 10)	5 (3, 8)	18 (11, 28)	17 (10, 27)	-	-	-	-
Bibevski S 2020 (case-series)	-	-	-	-	-	-	-	-

SR&MA, systematic review & meta-analysis; RCT, randomised controlled trial; ICU, intensive care unit; hrs, hours; WMD, weighted mean difference; CI, confident interval

5.4 ECONOMIC IMPLICATION

The cost-effectiveness of Custodiol HTK for myocardial protection has not yet been formally evaluated and the first study to look closely at the financial analysis of the solution was performed by Hummel BW et al. (2016) at Lee Memorial Health System, Florida from July 2011 through March 2015. In this single-institution retrospective case-control review, they compared the use of Custodiol HTK with traditional blood cardioplegia in 362 matched patients undergoing minimally invasive and open valve surgery. Charges incurred during the patient's stay were categorized as such: open heart ICU, surgical progressive care unit, operating room (all surgery and perfusion), anaesthesia, pharmacy (cardioplegia solutions), supplies (surgical implants), and others (radiology, cardiology, physical or occupational therapy, and clinical laboratories). The study demonstrated that administration of Custodiol HTK resulted in lower charges in every category except for pharmacy charges; the cost of blood cardioplegia solution is on average USD 400 less per patient. According to the figures, overall savings for the hospital by using Custodial HTK was USD 3,013 per patient (**Table 5**). In 2014, 300 patients had valve surgery and if applied for each patient, the hospital would have appreciated a savings of USD 903,900 using solely Custodiol HTK.[17, level II-2]

Table 5: Average variable charges comparison

	Total Charges	Open Heart ICU	SPCU	Operating Room	Anesthesia	Pharmacy	Supplies	Other
Custodiol	$19,671	$1841	$1355	$2428	$426	$1942	$9691	$1988
Traditional	$22,684	$2209	$1613	$2810	$558	$1543	$11,436	$2515
Custodiol savings	13.3%	16.7%	16.0%	13.6%	23.7%	−25.9%	15.3%	21.0%

ICU, Intensive care unit; SPCU, surgical progressive care unit.

5.5 LIMITATIONS

We acknowledge some limitations in our review and these should be considered when interpreting the results. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the report, which may have excluded some relevant articles and further limited our study numbers. The overall quality of available evidence which largely limited to small population size and retrospective, single-centre case-control/ case series or meta-analyses thereof, is poor and subject to significant bias. The non-randomised nature of such study also limits its validity. Indeed, there is wide variation in cardioplegia strategy and methodologic issues limit the degree to which results of these solutions can be accurately compared. Standardization of procedure elements and training, pursuit of randomised multicentre trials comparing directly to blood cardioplegia is all urgently needed.

6.0 CONCLUSION

Despite its widespread clinical use, data on the efficacy and safety of Custodiol HTK solution in both adult and paediatric patients undergoing diverse high-risk cardiac surgeries or procedures remain limited. Nevertheless, the retrievable evidence suggests that Custodiol HTK and blood cardioplegia were equivalent in terms of early clinical outcomes for myocardial protection in adult and paediatric populations. Both cardioplegia strategies had similar rate for myocardial infarction (MI) which includes both electrocardiogram-defined and the release of cardiac enzyme (CK-MB, troponin-I, troponin-T, lactate), low cardiac output syndrome (LCOS) defined by the need for inotropic and/or intra-aortic balloon pump support, rhythm disturbances (ventricular fibrillation [VF] as the first rhythm after cross-clamp release and new postoperative atrial fibrillation [AF]), blood transfusion or blood product use, and the duration of cardiopulmonary bypass (CPB) and aortic cross-clamping. In contrast to this, a single dose Custodial HTK compared favourably with traditional repetitive blood cardioplegia with regard to less severe endothelial injury and incidence of postoperative segmental wall motion abnormalities (SWMA), and shorter mechanical ventilation time. Above all, the similar rate of mortality and postoperative complications confirms the safety of the Custodial HTK in comparison to conventional cardioplegia. Lengths of ICU and hospital stay as well as the readmission rate were also comparable between the two strategies. Nonetheless, given the current available evidence with an acceptable safety profile and potential financial benefits, Custodiol HTK could be considered as feasible option and may be used as an effective substitute for blood cardioplegia to enhance myocardial protection in cardiac surgery.

7.0 REFERENCES

1. Bae YS, Kim Y, Kim JH et al. Independent functioning of cytosolic phospholipase A2 and phospholipase D1 in Trp-Lys-Tyr-Met-Val-D-Met-induced superoxide generation in human monocytes. J Immunol. 2000;164(8): 4089-4096
2. Mentzer RM. Myocardial protection in heart surgery. J Cardiovasc Pharmacol Ther. 2011; 16(3-4): 290-297.
3. Yamamoto H, Yamamoto F. Myocardial protection in cardiac surgery: a historical review from the beginning to the current topics. Gen Thorac Cardiovasc Surg. 2013; 61: 485-696
4. Karthik S, Grayson AD, Oo AY et al. A survey of current myocardial protection practices during coronary artery bypass grafting. Ann R Coll Surg Engl. 2004; 86: 413-415
5. Nardi P, Vacirca SR, Russo M et al. Cold crystalloid versus warm blood cardioplegia in patients undergoing aortic valve replacement. J Thorac Dis. 2018; 10:1490-1499
6. Fridell JA, Mangus RS, Tector AJ. Clinical experience with histidine-tryptophan-ketoglutarate solution in abdominal organ preservation: a review of recent literature. Clin Transplant. 2009; 23: 305-312
7. Braathen B, Jeppsson A, Scherste´n H et al. One single dose of histidine–tryptophan-ketoglutarate solution gives equally good myocardial protection in elective mitral valve surgery as repetitive cold blood cardioplegia: A prospective randomized study. J Thorac Cardiovasc Surg. 2011; 141: 995-1001
8. Liu J, Feng Z, Zhao J et al. The myocardial protection of HTK cardioplegic solution on the long-term ischaemic period in pediatric heart surgery. ASAIO J. 2008; 54: 470-473
9. Chambers DJ. Mechanisms and alternative methods of achieving cardiac arrest. Ann Thorac Surg. 2003; 75: S661-S666
10. Bretschneider HJ. Myocardial protection. Thorac Cardiovasc Surg. 1980; 28: 295-302
11. K192408 - US Food and Drug Administration. Available at https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192408.pdf Accessed on 28.04.2021
12. Edelman JJ, Seco M, Dunne B et al. Custodiol for myocardial protection and preservation. A systematic review. Ann Cardiothorac Surg. 2013; 2(6): 717-728
13. Reynolds AC, Asopa S, Modi A et al. HTK versus multidose cardioplegias for myocardial protection in adult cardiac surgery: A meta-analysis. J Card Surg. 2021; 36: 1334-1343
14. Mercan I, Dereli Y, Topcu C et al. 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(5): 634-643

15. Ali I, Hassan A, Shokri H et al. Efficacy of Histidine-Tryptophan-Ketoglutarate solution versus blood cardioplegia in cardiac surgical procedures: a randomized controlled | parallel group study. Heart Surg Forum. 2021; 24(1): E170-E176
16. Prathanee S, Kuptanond C, Intanoo W et al. Custodial-HTK solution for myocardial protection in CABG patients. J Med Assoc Thai. 2015; 98 (7): S164-167
17. Hummel BW, Buss RW, DiGiorgi PL et al. Myocardial protection and financial considerations of Custodiol cardioplegia in minimally invasive and open valve surgery. Innovations. 2016; 11(6): 420-424
18. Savini C, Murana G, Di Eusanio M et al. Safety of single-dose histidine-tryptophan-ketoglutarate cardioplegia during minimally invasive mitral valve surgery. Innovations. 2014; 9(6): 416-420
19. Pizano A, Montes FR, Carreño M et al. Histidine-Tryptophan-Ketoglutarate solution versus blood cardioplegia in cardiac surgery: A propensity-score matched analysis. Heart Surg Forum. 2018; 21(3): E158-E164
20. Fang Y, Long C, Lou S et al. Blood versus crystalloid cardioplegia for pediatric cardiac surgery: a meta-analysis. Perfusion. 2014; 30: 529-536
21. Allen BS. Pediatric myocardial protection: Where do we stand? J Horac Cardiovasc Surg. 2004; 128: 11-13
22. Mylonas KS, Tzani A, Metaxas P et al. Blood versus crystalloid cardioplegia in pediatric cardiac surgery: a systematic review and meta-analysis. Pediatr Cardiol. 2017; 38(8): 1527-1539
23. 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: 818
24. Qulisy EA, Fakiha A, Debis RS et al. Custodiol versus blood cardioplegia in pediatric cardiac surgery, two-center study. Journal of the Egyptian Society of Cardio-Thoracic Surgery. 2016; 24: 38-42
25. Bibevski S, Mendoza L, Ruzmetov M et al. Custodiol cardioplegia solution compared to cold blood cardioplegia in pediatric cardiac surgery: a single-institution experience. Perfusion. 2020; 35(4): 316-322

8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVID MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (R) 1946 to Mar 2021.

1. Cardiac Surgical Procedures/
2. (Procedure* adj1 (heart surgical or cardiac surgical)).tw.
3. Cardiovascular Surgical Procedures/
4. (Cardiovascular adj1 surgical procedure*).tw.
5. Cardioplegic Solutions/
6. Custodial HTK solution.tw.
7. Intracellular solution.tw.
8. 1 or 2 or 3 or 4
9. 5 or 6 or 7
10. 12 and 13

Other Databases

PubMed INAHTA US FDA	Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

Evidence Table : Efficacy/ safety/ organisational (ADULT)
Question : What is the efficacy, safety, and organisational issue related to the use of Custodiol HTK solution as replacement of blood cardioplegia in various cardiac surgeries?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
1. Edelman JJ, Seco M, Dunne B et al. Custodiol for myocardial protection and preservation. A systematic review. Ann Cardiothorac Surg. 2013; 2(6): 717-728	**Systematic review and meta-analysis** Electronic searches were performed of six databases; studies that compared Custodiol with conventional cardioplegia in adult patients undergoing cardiac surgery were identified for meta-analysis and large case series that reported results using Custodiol were also analysed. The primary end-point was mortality at 30 days. Secondary endpoints included surrogates for myocardial protection (myocardial infarction [MI], cardiac enzyme release, low cardiac output syndrome [LCOS]/ use of inotropes) and rhythm disturbances (ventricular fibrillation [VF] as the first rhythm after cross clamp release, and new post-operative atrial fibrillation [AF]).	II-2	Fourteen out of 22 comparative studies were selected for quantitative meta-analysis (n=2,114) and eight large case-series were examined for qualitative appraisal (n=6,840).	Custodiol HTK	Conventional cardioplegia (blood or extracellular crystalloid)	-	**Primary endpoint – mortality** Overall, patients receiving Custodiol had a similar risk of mortality as patients receiving conventional cardioplegia for myocardial protection. The rate of mortality was 2.70% in the Custodiol group, compared with 2.63% in the conventional group (RR 1.05, 95% CI 0.59 to 1.88; p=0.86). No significant difference in the rates of mortality as reported in eight large cases-series. **Secondary endpoints - myocardial protection** The rate of MI reported in patients given Custodiol did not differ from patients receiving conventional cardioplegia (Custodiol 2.81% versus 1.62%, RR 1.72, 95% CI 0.82 to 3.60; p=0.15). Mean differences for both creatine kinase myocardial band (CK-MB) and troponin-I (Tn-I) did not differ between groups (CK-MB: mean difference [MD] -4.15 (95 CI -12.41 to 4.10; p=0.32; Tn-I: MD 0.90, 95% CI -4.68 to 6.48; p=0.75). The rate of inotropes/ LCOS did not differ between groups (Custodiol 15.0% versus conventional 12.7%, RR 1.33, 95% CI 0.86 to 2.05; p=0.20). There was a trend for increased incidence of ventricular arrhythmias during reperfusion that reached statistical significance in the fixed but not the random effects model (Custodiol 20.1% versus 9.7%, random effects RR 1.84, 95% CI 0.91 to 3.74; p=0.09; fixed effects RR 2.12, 95% CI 1.63 to 2.76; p<0.001). There was no significant difference in the rate of AF between groups (Custodiol 34.3% versus conventional 17.7% RR 1.36, 95% CI 0.74 to 2.50; p=0.32). There was a trend towards shorter cross-clamp time in the conventional cardioplegia groups (weighted mean: Custodiol 62.9 min versus conventional 54.8 min; p=0.11).	Assessment of quality of included studies not reported.

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2. Reynolds AC, Asopa S, Modi A et al. HTK versus multidose cardioplegias for myocardial protection in adult cardiac surgery: A meta-analysis. J Card Surg. 2021; 36: 1334-1343	**Systematic review and meta-analysis** Electronic searches were performed of three databases; included trials (RCT) were those that directly compared the use of HTK versus any other type of multidose cardioplegias (MDC) in open-heart surgery. All analyses were conducted using Comprehensive Meta-Analysis (CMA) version 3. The primary outcomes analysed were cardiopulmonary bypass (CPB) time, aortic cross-clamp time, spontaneous defibrillation (spontaneous return of heartbeat), inotropic support, mortality, atrial fibrillation (AF), creatine kinase muscle brain band (CK-MB), and troponin I (Tn-I). The risk of bias was assessed using a modified Jadad scale for RCTs. Publication bias was investigated using funnel plots.	I	Seven RCTs included in the analysis had an aggregate of 804 participants with either coronary artery disease or valvular disease, 412 of whom were HTK patients versus 391 who received MDC.	Custodiol HTK	MDC (blood or extracellular crystalloid)	-	Spontaneous defibrillation following aortic cross-clamp removal significantly favoured HTK (odds ratio [OR] 2.809, 95% CI 1.574 to 5.012; $p<0.01$). There were no other notable significant differences between HTK and MDC in any of the parameters measured: **CPB time (7 studies; n=444)** The overall mean difference (MD) was 2.103 min (95% CI −2.329 to 6.536; p=0.352). **Aortic cross-clamp time (7 studies; n=668)** The overall MD was 0.276 min (95% CI −2.569 to 3.120; p=0.849). **Inotropic support (4 studies; n=306)** The OR was 1.5 (95% CI 0.742 to 3.032; p=0.259). **Mortality (3 studies; n=285)** The OR was 1.237 (95% CI 0.385 to 3.978; p=0.721). **AF (4 studies; n=306)** The OR was 0.809 (95% CI 0.511 to 1.281; p=0.366). **Release of CK-MB (5 studies; n=335)** The standardized mean difference (SMD) was −0.046 (95% CI −0.27 to 0.178; p=0.687). **Release of Tn-I (3 studies; n=285)** The MD was −1.424 ng/ml (95% CI −7.747 to 4.898; p=0.659).	Jadad scale (median 4): moderate quality. None of the studies performed blinding; only one used an intention to treat analysis. No studies had incomplete data.

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3. Mercan I, Dereli Y, Topcu C et al. 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(5): 634-643	**Randomised controlled trial** A total of 50 patients who underwent isolated coronary artery bypass surgery between March 2018 and May 2018 were randomly divided into two groups: group 1 (Bretschneider's HTK solution, n=25) and group 2 (cold blood cardioplegia, n=25). Data related to the indicators of endothelial dysfunction were recorded. Flow-mediated dilation (FMD) was measured together with the assessment of the values of endothelin-1 (ET-1), von Willebrand factor (vWF), lactate, and asymmetric dimethylarginine (ADMA) to identify endothelial dysfunction. Then, the two groups were compared regarding these values. All data except FMD were recorded preoperatively (T0), and at day 0 (T1), day 1 (T2), day 3 (T3), and day 5 (T4) during the postoperative period.	I	A total of 50 patients with no gender preference (between 40 and 80 years) whom an isolated coronary artery bypass grafting (CABG).	Bretschneider's (Custodiol) HTK solution	Cold blood cardioplegia (CBC)	Preoperatively (T0), and at day 0 (T1), day 1 (T2), day 3 (T3), and day 5 (T4)	**Levels of endothelial dysfunction indicators according to the time points together with the comparison of the two cardioplegia groups** Asymmetric dimethylarginine (ADMA), vWF, ET-1, FMD, and lactate levels were compared with two-way ANOVA for mixed measured for both groups. A significant difference was found between five different measurements of four indicators ($p=0.001$) and three measurements of one indicator (FMD) ($p<0.001$). Endothelin-1 (ET-1) levels were significantly different between the groups ($p=0.002$). Indicator-group interaction was present for vWF and ET-1 levels ($p=0.043$ and $p=0.001$, respectively). Lactate levels were higher in HTK group than in CBC group. However, this difference was not statistically significant ($p=0.301$). The FMD level was statistically significantly higher in the HTK group compared to the CBC group at time points T2 and T4 ($p=0.002$). **Safety** There was no significant difference between Bretschneider's HTK and CBC groups in terms of postoperative complications which included pulmonary (postoperative atelectasis, exacerbation of COPD, pulmonary edema), antibiotic revision, temporary arrhythmia, neurologic, renal (temporary urea and creatinine elevation), and gastrointestinal complications (dyspepsia). Mortality was not observed in any of the 50 patients included in the study. **Organization** There was no significant difference between the two groups in terms of total drainage, postoperative blood product use (erythrocyte suspension), mean inotropic agent requirement, extubation time, and ICU stay.	Small sample size

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4. Ali I, Hassan A, Shokri H et al. Efficacy of Histidine-Tryptophan-Ketoglutarate solution versus blood cardioplegia in cardiac surgical procedures: a randomized controlled | parallel group study. Heart Surg Forum. 2021; 24(1): E170-E176	**Randomised controlled trial** Patients were randomly allocated into two groups (HTK and blood cardioplegia), according to a computer-generated randomisation code, with an allocation ratio of 1:1. Randomisation was done by a statistician who was not involved in the study using the SAS statistical package version 9.3. Opaque sealed envelopes were prepared, according to the randomisation schedule and were opened by a clinician not involved in any part of the study. The primary outcome was the 30-day mortality rate. Secondary outcomes included cardiac enzyme levels [troponin >20 mg/l, CK-MB >30 U/l] 12 and 24 h postoperatively, segmental wall motion abnormalities (SWMAs), and at least two new Q waves on two consecutive electrocardiograms and pericardial effusion, electrocardiographic changes such as ventricular fibrillations or ventricular arrhythmia, cross-clamp and total bypass time, length of ICU stay and hospital stay, requirement for inotropic support, 30-day readmission, intra-aortic balloon use and the incidence of late postoperative complications (renal failure).	I	A total of 320 patients aged 30-70 years old undergoing various cardiac surgeries.	Custodiol HTK	Blood cardioplegia	-	**Patient demographics/ preoperative results** The two groups were similar in terms of their demographic and preoperative data. The total bypass and cross-clamp time were significantly longer in the blood cardioplegia group compared with the HTK group (both $p<0.001$). **Preoperative and postoperative echocardiography** Preoperative and postoperative ejection fractions were comparable between the two study groups ($p=0.380$ and $p=0.885$, respectively). There was no significant difference between the two groups, in terms of the SWMA at preoperative echocardiography ($p=0.073$). In contrast, SWMAs at postoperative echocardiography were significantly higher in the blood cardioplegia than the HTK ($p=0.008$). The incidence of pericardial effusion was similar between the two groups ($p=0.090$). **Intraoperative results** The number of patients requiring DC Shock was significantly higher in the HTK than in the blood cardioplegia ($p<0.001$). Conversely, the number of patients requiring inotropic support was significantly higher in the blood cardioplegia than in the HTK ($p<0.001$). **Postoperative results** The lengths of ICU and hospital stay were significantly longer in the blood cardioplegia than in the HTK ($p=0.004$ and $p<0.001$, respectively). The ventilation time was significantly longer in the blood cardioplegia than in the HTK ($p<0.001$). There was no significant difference between the two groups, in terms of electrocardiographic changes ($p=0.176$) and cardiac enzyme levels 12 and 24 h postoperatively ($p=0.317$ and $p=0.239$, respectively). **Postoperative complications** The 30-day mortality, 30-day readmission, incidence of renal failure and postoperative complications were comparable between the two groups, except that the occurrence of prolonged ventilation time was significantly higher in the blood cardioplegia group.	

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5. Prathanee S, Kuptanond C, Intanoo W et al. Custodial-HTK solution for myocardial protection in CABG patients. J Med Assoc Thai. 2015; 98 (7): S164-167.	**Retrospective case-control** Retrospective case-control study in CABG patients were reviewed in Cardiovascular and Thoracic Unit, Department of Surgery, Khon Kaen University during April 2011 and September 2012. Baseline data such as age, sex, NYHA, risk factors, associated disease, operation, CPB and aortic cross clamp time, complication, defibrillation after surgery, ICU stay, and mortality rate were analysed.	II-2	One hundred and twenty-five patients who underwent triple vessels coronary artery disease (TVD) and had performed CABG were divided into groups A and B, for myocardial protection by blood cardioplegia (n=60) and Custodiol HTK (n=65). Exclusion criteria were previous CABG, emergency surgery, LVEF less than 20% and acute myocardial infarction within 30 days.	Custodiol HTK	Blood cardioplegia	-	**Intraoperative variables** CPB and aortic cross clamp time were significantly longer in the blood cardioplegia group compared with the HTK group (p=0.027 and p=0.046, respectively). **Postoperative variables** Ventricular fibrillation (VF) after removal of aortic cross clamp occurred more frequently in Custodiol-HTK group (33.8% versus 8.3%; p=0.001). There were no differences between the two groups in the rate of renal failure needed dialysis, new heart failure, pulmonary and GI complication, mortality, ICU and post-operative hospital stay. **Authors conclusion:** There was significantly more spontaneous ventricular fibrillation after release of cross clamping in HTK group. Clinical outcome of single doses of antegrade, cold Custodiol-HTK cardioplegia solution in CABG surgery protected the myocardium equally well.	

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6. Hummel BW, Buss RW, DiGiorgi PL et al. Myocardial protection and financial considerations of Custodiol cardioplegia in minimally invasive and open valve surgery. Innovations. 2016; 11(6): 420-424	**Retrospective case-control with cost analysis** A single-institution, retrospective case-control review was performed on patients who underwent valve surgery in Lee Memorial Health System at either Health Park Medical Center or Gulf Coast Medical Center from July 1, 2011, through March 7, 2015. A total of 181 valve cases (aortic or mitral) performed using Custodiol HTK cardioplegia were compared with 181 cases performed with traditional blood cardioplegia. Outcomes were queried on the matched patients, and data were collected for intraoperative/ postoperative blood transfusion, postoperative atrial fibrillation, prolonged ventilation, ICU readmission, hospital readmission (≤30 days), permanent stroke, postoperative length of stay (LOS), peak troponin I, reoperation for bleeding, and operative mortality (mortality within 30 days from surgery). **Financial analysis** Charges incurred during the patient's stay were categorized as such: open heart ICU, surgical progressive care unit, operating room (all surgery and perfusion), anaesthesia, pharmacy (cardioplegia solutions), supplies (surgical implants), and others (radiology, cardiology, physical or occupational therapy, and clinical laboratories).	II-2	A total of 181 matched pairs were identified for a total of 362 patients who received minimally invasive or open valve surgery, MIVS (aortic valve replacement or mitral valve repair/ replacement). Of the 181 pairs, 94 pairs were identified as undergoing MIVS via right thoracotomy. Of these, 53 were minimally invasive aortic valve replacements (right chest or upper sternotomy) and 41 were right chest mitral valve repair or replacement.	Custodiol HTK	Blood cardioplegia	-	Analysis was completed on the 362 patients who underwent valve surgery by either full sternotomy or minimally invasive approach (right chest or partial sternotomy). The two groups had matching preoperative clinical factors. Patients had similar outcomes including postoperative atrial fibrillation, prolonged ventilation, ICU readmission, postoperative LOS, postoperative peak troponin, reoperation for bleeding, and operative mortality. The Custodiol group had statistically significant improvement in blood transfusion ($p<0.03$), permanent stroke ($p<0.04$), and hospital readmission rate ($p<0.01$). Subgroup analysis was performed for patients undergoing MIVS via right thoracotomy (94 patients using Custodiol versus 94 patients using blood cardioplegia). There were no statistically significant differences in outcomes with the exception of hospital readmission rates that were lower in the Custodiol group. Subgroup analysis was also performed in patients that had aortic valve replacement through a right thoracotomy (53 patients using Custodiol versus 53 patients using blood cardioplegia) and no statistically significant differences in the outcome categories. **Financial analysis** Administration of Custodiol HTK cardioplegia resulted in lower charges in every category except for pharmacy charges. The cost of blood cardioplegia is on average USD 400 less per patient. Overall savings for the hospital by using Custodial cardioplegia was USD 3,013 per patient. In 2014, 300 patients had valve surgery in the Lee Memorial Health System. If applied for each patient, the hospital would have appreciated a savings of USD 903,900 using solely Custodiol HTK.	Subject to significant selection bias

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7. Savini C, Murana G, Di Eusanio M et al. Safety of single-dose histidine-tryptophan-ketoglutarate cardioplegia during minimally invasive mitral valve surgery. Innovations. 2014; 9(6): 416-420	**Retrospective case-series** Between February 2003 and October 2012, a total of 49 consecutive patients underwent minimally invasive mitral valve surgery using a single dose of HTK solution for myocardial protection. Primary outcomes included hospital mortality, low cardiac output syndrome (LCOS) (defined by the need for inotropic and/or intra-aortic balloon pump support), myocardial infarction (MI) [which includes both electrocardiogram-defined (ECG-defined) and/or enzyme-defined MI], and rhythm disturbances [ventricular fibrillation (VF) after cross-clamp release and new postoperative atrial fibrillation (AF)]. Venous blood samples were collected before the operation as well as 6, 12, 24, and 48 hours postoperatively. A 12-lead ECG was recorded before surgery; at 1 hour and 6 hours postoperatively; as well as on the first, the second, and the seventh day after the operation.	II-2	Out of 49 patients, 25 were men (71.8%), and the mean (SD) age was 61.1 (9.3) years. The preoperative ejection fraction was normal in all patients [63.7 (8.4)], two patients had peripheral vascular disease, two had chronic obstructive pulmonary disease, and two had cerebrovascular disease. Mitral valve insufficiency (83.67%), rheumatic mitral valve stenosis disease (4.08%), and functional mitral regurgitation (2.04%) represented the main indications to surgery.	Custodiol HTK	-		Intraoperatively, the mitral valve was repaired in 44 cases (89.8%) and replaced in five cases (10.2%). The mean (SD) CPB time was 148.6 (45) minutes, and aortic cross-clamp duration was 97.9 (45) minutes. The heart, after removal of the cross-clamp, restarted spontaneously in 37 cases (75.5%), and ventricular arrhythmias requiring electrical cardioversion to sinus rhythm occurred in the remaining 12 cases (24.5%). The incidence of AF in the postoperative period occurred in 12 patients (24.49%). There were no operative/ hospital deaths or major postoperative complications. At 3, 12, and 24 hours after surgery, no significant modifications in myocardial cytonecrosis enzymes were found, regardless of cross-clamp time duration (>100 or <100 minutes). Consistently, no ischaemic ECG modifications were observed before discharge. None of the patients developed LCOS postoperatively, and only five patients (10.2%) needed mild-to-moderate postoperative inotropic support. The overall frequency of postoperative neurologic events and acute renal dysfunction was 2% (n=1) and 0%, respectively. The mean (SD) assisted ventilation time was 9.3 (15.9) hours and the mean (SD) ICU stay was 1.69 (1.44) days.	Limitation: retrospective design and small population size

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8. Pizano A, Montes FR, Carreño M et al. Histidine-Tryptophan-Ketoglutarate solution versus blood cardioplegia in cardiac surgery: A propensity-score matched analysis. Heart Surg Forum. 2018; 21(3): E158-E164	**Quasi experimental study** This study was a single centre retrospective review of prospectively collected data. Between January 2008 and December 2015, 4,480 patients underwent cardiac surgery using cardiopulmonary bypass (CPB) and cardioplegic arrest. The primary end-point was ICU length of stay (LOS). Secondary end points included aortic cross-clamp time, CPB time, changes in serum sodium concentration, readmission to ICU, 30-day hospital readmission, 30-day mortality, blood product usage, and the incidence of major postoperative complications (prolonged [>24 h] mechanical ventilation, acute renal failure, new onset dialysis, clinical stroke, re-exploration for bleeding, deep sternal wound infection or post-operative intra-aortic balloon pump [IABP] implantation).	II-2	Patients were divided into a blood cardioplegia group (n=3,852) and an HTK solution group (n=628). Propensity score matching was used to adjust for differences between the two groups, and 292 matched pairs were identified.	Custodiol HTK	Blood cardioplegia with St Thomas No 2 solution	-	**Characteristics and clinical outcome: unmatched cohort** A differences in demographic characteristics and comorbid diseases between the two groups were noted. The blood cardioplegia group was significantly older, and consisted of a greater number of men with a higher prevalence of hypertension, diabetes, dyslipidaemia, history of myocardial infarction, and slightly lower values of ejection fraction. Active endocarditis, congestive heart failure, and higher values of creatinine were more prevalent in the HTK solution group. The unmatched blood cardioplegia cohort included more urgent/ emergent operations (62% versus 52%; p<0.001) and a lower percentage of redo procedures (4.9% versus 17%; p<0.001). Regarding the procedures performed, valvular surgery of any kind (aortic, mitral or tricuspid) was more common in the HTK solution group (88.2% versus 31.7%, p<0.001), whereas CABG surgery was more common in the blood cardioplegia group (20.9% versus 65.3%, p<0.001). **Characteristics and clinical outcomes: propensity score-matched patients** No significant differences were found between the matched groups with regard to demographic characteristics or type of procedures performed. Regarding intraoperative variables, the HTK group had shorter aortic cross-clamp times (98.5 ± 39 versus 116.1 ± 38 min; p<0.001) and shorter CPB times (132.8 ± 53 versus 147 ± 47 min; p=0.001). Following cardioplegia delivery, patients in the HTK group showed a significant decrease in serum sodium concentration during CPB compared to patients who received blood cardioplegia. The serum sodium concentration returned to normal values on the first postoperative day. In the HTK solution group, 87 (30%) patients required a second dose of cardioplegia due to return of electrical activity. No patients required a third dose of HTK solution. Regarding the primary study endpoint, the ICU LOS did not differ between groups matched by propensity score. Furthermore, no significant differences were found in any secondary outcome variables.	

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9. Mylonas KS, Tzani A, Metaxas P et al. Blood versus crystalloid cardioplegia in pediatric cardiac surgery: a systematic review and meta-analysis. Pediatr Cardiol. 2017; 38(8): 1527-1539	**Systematic review and meta-analysis** A systematic literature search of the PubMed and Cochrane databases was performed with respect to the PRISMA statement. Data were appropriately pooled using random and mixed effects models. The modified Jadad scale was used to assess the risk of bias of included RCTs and Newcastle–Ottawa Quality scale for non-RCT. The following outcomes were assessed as **dichotomous variables**: postoperative extracorporeal membrane oxygenation (ECMO) implementation, postoperative complications, reoperations, and 30-day mortality rate; and **continuous variables**: cardiac troponin I (cTnI) immediately after reperfusion (cTnI-0 h) and 1 h (cTnI-1 h), 4 h (cTnI-4 h), 12 h (cTnI-12 h), and 24 h (cTnI-24 h) postoperatively, lactate levels preoperatively (Lac-pre), lactate levels immediately after reperfusion (Lac-0 h), as well as 1 h (Lac-1 h) and 12 h (Lac-12 h) postoperatively, ATP before (ATP-pre) and after reperfusion (ATP-post) aortic cross-clamp time, cardiopulmonary bypass (CPB) time, circulatory arrest time, significant inotropic support time, mechanical ventilation time, ICU length of stay, and length of hospital stay.	II-2	In total, 7,711 pediatric patients (56 studies) underwent cardiac surgery using either blood (n=6,289) or crystalloid cardioplegia (n=1,422) over a 40-year period (1973–2014). A meta-analysis of the 10 eligible studies directly comparing BCP (n=416) to CCP (n=281) was also performed.	Crystalloid cardioplegia (CCP)	Blood cardioplegia (BCP)	-	**Cardiac troponin I (cTnI), lactate, and ATP levels** No significant difference between the two groups with regard to cTnI and Lac at any measured time point. However, pooled analysis of available data found significantly higher ATP-pre levels in the CCP group ((WMD -6.44 nmol/mg, 95% CI -8.33 to-4.55) but not ATP level after reperfusion. However, there was significantly lower cTnI-4 h in the blood cardioplegia cohort compared to the crystalloid cohort (WMD: -1.62 ng/ml, 95% CI -2.07 to -1.18). **Intraoperative outcomes** No difference was found between blood and crystalloid cardioplegia with regard to aortic cross-clamp, CPB, and circulatory arrest time. **Postoperative complications** No statistically significant difference was identified in terms of either rhythm disturbances or AV blocks, postoperative incidence of heart or respiratory failure, and the need for peritoneal dialysis between the two study arms. Additionally, the rate of reoperation was not significantly higher in the CCP group compared to BCP. **Postoperative outcomes** No difference was seen between the two cohorts on mechanical ventilation time (WMD -10.12 h, 95% CI -24.47 to 4.24), postoperative need for ECMO or with regard to significant inotropic support, length of ICU stay (WMD -0.08 days, 95% CI -1.52 to 1.36), and length of hospital stay (WMD 0.13 days, 95% CI -0.85 to 1.12).	Only six comparative RCTs, which involved a relatively small number of patients.

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10. 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: 818	**Randomised controlled trial** Patients were randomly allocated to three groups solutions (each one 20) for pediatric cardiac surgery at Cairo National Heart Institute (from June 2015 to October 2017). All patients were subjected to a preoperative clinical examination and routine preoperative laboratory investigations. Radiological examination in the form of chest x-ray and echocardiography was also done. Hemodynamic parameters, duration of cardiopulmonary bypass (CPB), aortic cross clamping and the whole surgical duration, mechanical ventilation duration and the length of ICU stay were measured. Venous blood samples were collected for measurement of cardiac marker proteins (CK-MB) and troponin T. Uses of inotropic support were also recorded. One-way ANOVA test and Chi-square test were used.	II-1	A total of 60 children aged 3-10 years of either sex who underwent elective cardiac surgery for acyanotic heart diseases using CBP.	Custodiol HTK (Group A, n=20) Blood cardioplegia (Group B, n=20) Crystalloid (St. Thomas) cardioplegia (Group C, n=20)	Between intervention	-	No statistically significant different between the study groups regarding the demographic data. The hemodynamic variables (heart rate, arterial blood pressure, peripheral oxygen saturation measured before and all over the duration of operation) and central venous pressure (baseline, before and after CPB, at the end of the operation and every 6 h in the ICU or when indicated) showed no statistically significant different between the study groups. Duration of CPB, aortic cross clamp time and the whole surgical duration were also not statistically significant. Regarding extubation time, time of mechanical ventilation, and length of ICU stay, there were statistically significant differences between the three study groups with the longest time was in the group B and the shortest in the group A. There were 1.5 ± 0.4 hrs, 5.2 ± 0.8 hrs, 17.1 ± 0.3 hrs in group A; 5.1 ± 0.6 hrs, 8.5 ± 1.1 hrs, 58.8 ± 10.9 hrs in group B; and 3.3 ± 1.2 hrs, 6.9 ± 1.8 hrs, 55.9 ± 10.6 hrs in group C. There was statistically significant difference between the study groups regarding the use of inotropic support with highest percentage (100%) of use in group A, followed by 90% for group C and lowest percentage for group B. Troponin T levels recorded at 6 and 12 hrs after the operation were not statistically significant difference among the study groups except that recorded 24 hrs; the highest level was in the group B (28.1 ± 2.4 ng/ml) and the lowest in group C (24.5 ± 3 ng/ml). CK-MB levels was also not statistically significant different among the study groups except that recorded after 12 hrs; the highest was in group C (147.8 ± 28.1 ng/ml) and the lowest in group B (128.2 ± 24. ng/ml 6).	A relatively small sample size. The surgeons were not blind to which type of cardioplegia was being used.

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11. Qulisy EA, Fakiha A, Debis RS et al. Custodiol versus blood cardioplegia in pediatric cardiac surgery, two-center study. Journal of the Egyptian Society of Cardio-Thoracic Surgery. 2016; 24: 38-42	**Retrospective cohort** A multi-centred, retrospective review was conducted at two institutions. Patients were identified from a prospective database and additional data were collected from operative report and electronic and paper charts. Patients were then divided into two groups on the basis of the cardioplegia solution used. A composite endpoint of all cause death, low cardiac output syndrome (LCOS), acute kidney injury (AKI), and significant arrhythmia was analysed with a multiple logistic regression model adjusted for complexity using the Risk Adjustment of Congenital Heart Surgery-1 (RACHS-1) categories. Length of ICU and hospital stay in days were also reported.	II-2	A total of 154 children (1 day to 18 years of age) who underwent congenital heart surgery with the use of cardiopulmonary bypass and cardioplegia between November 2013 and June 2014.	Custodiol HTK (n=66)	Blood cardioplegia (n=88)	-	In an unadjusted outcomes, patients receiving Custodiol had longer mechanical ventilation (MV) times compared to blood cardioplegia (median 72 versus 47 min; p=0.005). A trend was also noted for more prevalent LCOS (33% versus 23%; p=0.14). In the risk adjusted comparison of the composite outcome of all-cause death, LCOS, AKI and significant arrhythmia, Custodiol cardioplegia was found to be an independent predictor of an adverse outcome (OR 3.17, 95% CI 1.41 to 7.14; p=0.0054). **Authors conclusion:** Custodial cardioplegia is associated with less optimal myocardial protection and higher adverse outcomes compared to cold blood cardioplegia in children undergoing cardiac surgery.	The present study is limited by the retrospective nature of the analysis and the small number of patients.

Evidence Table : Efficacy/ safety/ organisational (PAEDIATRIC)
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12. Bibevski S, Mendoza L, Ruzmetov M et al. Custodiol cardioplegia solution compared to cold blood cardioplegia in pediatric cardiac surgery: a single-institution experience. Perfusion. 2020; 35(4): 316-322	**Retrospective case-series** Single-centre retrospective review including 133 patients <12 months old undergoing biventricular repair. Demographic and echocardiographic data were compared between the two groups.	II-2	Patients receiving Custodiol were slightly younger (100 ± 62 days) and lower weight (4.7 ± 1.3 kg) compared to 152 ± 86 days and 5.2 ± 1.3 kg for blood cardioplegia ($p<0.05$).	Custodiol HTK (n=106)	Blood cardioplegia (n=27)	-	The Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery Congenital Heart Surgery score was similar between both groups. Average cardiopulmonary bypass time was similar between both groups (Custodiol 93 ± 54 minutes versus blood 81 ± 44 minutes; p=0.46) as was aortic cross-clamp time (Custodiol 58 ± 33 minutes versus cold blood 53 ± 33 minutes; p=0.62). Preoperative left ventricular ejection fraction (LVEF) was similar for blood 73 ± 8% versus Custodiol 70 ± 9%; p=0.21. There was also no intergroup difference in LVEF 24 hours post-operative (blood 64 ± 9% versus Custodiol 65 ± 12%; p=0.53) or at discharge (blood 66 ± 10% versus Custodiol 66 ± 11%; p=0.95). The preoperative right ventricle function by fractional area change was also similar in blood cardioplegia (46 ± 13%) versus Custodiol (48 ± 9%; p=0.38) and showed similar drops in parameters in the two groups 24 hours after surgery and at discharge.	

e ISBN 978-967-2887-17-1

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