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ORIGINAL ARTICLE

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HTK versus multidose cardioplegias for myocardial protection in adult cardiac surgery: A meta-analysis

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Abstract

Background: Histidine–tryptophan–ketoglutarate (HTK) cardioplegia for myocardial protection obviates the need for maintenance cardioplegia doses, and thus allows for greater focus on procedure accuracy. The aim of this meta-analysis is to evaluate the safety and efficacy of HTK versus multidose cardioplegias during cardiac surgery in an adult population.

Methods: Electronic searches were performed using PubMed, Science Direct, and Google Scholar databases. The key search terms included HTK cardioplegia AND cardiac surgery AND adult. This was followed by a meta-analysis investigating cardiopulmonary bypass (CPB) duration, cross-clamp duration, spontaneous defibrillation, inotropic support, mortality, atrial fibrillation, creatine kinase muscle brain band (CK-MB) and troponin I (TnI).

Results: Seven randomized controlled trials ($n = 804$) were analyzed. Spontaneous defibrillation following aortic cross-clamp removal significantly favored HTK (odds ratio [OR], 2.809; 95% confidence interval [CI], 1.574 to 5.012; $I^2 = 0\%$; $p < .01$). There were no other notable significant differences between HTK and multidose cardioplegia in any of the parameters measured. In particular, the OR for mortality was 1.237 (95% CI, 0.385 to 3.978; $I^2 = 0\%$; $p = .721$) and the mean difference for CPB duration overall was 2.072 min (95% CI, −2.405 to 6.548; $I^2 = 74\%$; $p = .364$).

Conclusion: HTK is safe and effective during adult cardiac surgery when compared with multidose cardioplegias for myocardial protection during surgical correction of acquired pathology in the adult population. HTK may, therefore, be suitable for complex cases or those of extensive duration, without the prospect of increased postoperative morbidity or mortality.

KEYWORDS

adult, cardiac surgery, cardioplegia, HTK, multidose

1 | INTRODUCTION

Myocardial protection is of concern to the cardiac surgical team during cardiopulmonary bypass (CPB). CPB was first demonstrated by Gibbon in 1954 as a mechanism to prevent major organ ischemia during asystole. Protection was not, however, sustainable for the duration of complex cardiac correction procedures, with an upper range of postoperative in-hospital mortality of 65%.[1] Cardiac examination post-mortem revealed "stone heart"—irreversible myocardial contraction from ATP-mediated actin–myosin coupling, with failure of actin–myosin uncoupling due to ATP depletion.[2] This low level of success was thought to be associated with the high concentration of citrate leading to chelation of magnesium and calcium.[3] However, the idea of using moderately elevated potassium re-emerged in the 1970s.[3] One of the foremost proponents of crystalloid hyperkalemic cardioplegia was the Bretschneider group in Germany. In 1980, they devised the histidine–tryptophan–ketoglutarate (HTK) cardioplegia, which is the subject of this meta-analysis.[3]

HTK (branded as Custodiol® by Essential Pharmaceuticals LLC), has been presented by industry to surgeons as an alternative solution that exceeds other cardioplegias in myocardial protection.[4] This claim relies on the single-dose administration of HTK compared with other multidose cardioplegias (MDC), sparing time in the adjustment of equipment during cardioplegia re-administration, allowing greater time to operate and thus a decreased CPB duration.[5] Other benefits include a lower concentration of sodium, calcium, and potassium compared with other cardioplegias with cardiac arrest arising from the deprivation of sodium.[5] Finally, histidine is thought to aid buffering, mannitol and tryptophan to improve membrane stability, and ketoglutarate to help ATP production during reperfusion.[6]

This is the first meta-analysis to solely focus on HTK versus MDC during cardiac surgery in the adult-acquired disease population. A meta-analysis by Gambardella et al.[7] in 2019 claimed to investigate single dose versus MDC in the adult population; however, the inclusion of Careaga et al.[8] which contained both adult and pediatric populations reduces the applicability of their findings to the clinical landscape of adult cardiac surgery. Our meta-analysis also includes the findings of Vivacqua et al.[9] Vivacqua et al.[9] was submitted for publication 5 days after Gambardella et al.,[7] and so was not included in their analysis. In addition, our meta-analysis solely focuses on randomized controlled trials (RCTs; Gambardella'a included both RCTs and propensity-matched studies). Most importantly, we supply new data on more outcomes and include subgroup analysis according to surgery type.

It is, therefore, the aim of this meta-analysis to define and quantify the safety and efficacy of HTK to other cardioplegias during adult cardiac surgery.

2 | METHODS

This is a meta-analysis. A meta-analysis involves the pooling of data from already published trials. As such, therefore, no ethical approval and no informed consent is required.

As per many of our previous surgical data analyses,[10,11] this systematic review and meta-analysis was performed in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines (see Supporting Information files).

2.1 | Search strategy

To identify potential studies, systematic searches were carried out using PubMed, Science Direct, and Google Scholar. The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of "Custodiol versus Blood," "HTK solution versus blood," "Bretschneider's solution versus blood," "Custodiol versus crystalloid," "HTK versus crystalloid," "Bretschneider's solution versus crystalloid," AND "Cardiac Surgery" AND "Cardioplegia." (see Supporting Information file for the search strategy). All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until October 1, 2020. Data were extracted using predesigned extraction tables.

2.2 | Types of trials to be included and excluded

Included trials were those that directly compared the use of HTK versus any other type of MDC in open-heart surgery. There were no language restrictions. Animal studies and review papers were excluded. Studies that did not have any of the desired outcome measures were excluded. Incomplete data, or data from an already included study, were excluded. Other treatment modalities and interventions for coronary artery disease such as percutaneous coronary intervention and valvular disease such as transcatheter aortic valve intervention were excluded.

2.3 | Participants/population

This meta-analysis analyzed RCTs of both male and female adult (≥8 years) patients with either coronary artery disease or valvular disease who were undergoing cardiac surgery using either HTK or other types of MDC.

2.4 | Intervention(s) and exposure(s)

This meta-analysis considered all RCTs where HTK or another type of MDC were used in either coronary artery bypass graft (CABG) or in patients being treated for valvular disease. This specifically included all RCTs where the intention was to carry out cardiac surgery using HTK cardioplegia.

2.5 | Search results

Our initial search found 361 articles of which 330 were excluded on the basis of title and abstract and a further 14 duplicate studies were excluded. A further six studies were excluded as they were investigating

TABLE 1 Characteristics of included trials

Study	Surgery	Type of MDC	Temp. MDC	Delivery direction MDC	*N* HTK (MDC)	Age HTK (MDC)	% Male HTK (MDC)	Pooled outcomes
Arslan et al.[12]	CABG	Crystalloid	NR	Ante	21 (21)	60.2 ± 5.6 (60.4 ± 7.3)	72 (90)	CK-MB CPB time Cross-clamp time TnI
Beyersdorf et al.[13]	CABG	Blood	Cold	Ante	12 (12)	59 ± 8 (58 ± 7)	81 (66)	AF CK-MB CPB time Cross-clamp time Inotropic support Rate of spontaneous defibrillation
Braathen et al.[14]	Valvular	Blood	Cold	Ante	38 (38)	59 ± 2 (59 ± 2)	99 (90)	AF CK-MB CPB time Cross-clamp time Inotropic support Mortality
Demmy et al.[15]	CABG	Crystalloid	Cold	Ante	68 (68)	NR	90 (90)	AF CK-MB Inotropic support TnI
Gallandat Huet et al.[16]	CABG	Crystalloid	Cold	Ante	132 (117)	60.7 ± 8.8 (60.7 ± 7.6)	81 (80)	CPB time Cross-clamp time Mortality Spontaneous return of heartbeat
Gaudino et al.[17]	Valvular	Blood	Warm	Ante	31 (29)	64 ± 9 (61 ± 5)	81 (72)	CPB time Cross-clamp time Mortality
Kammerer et al.[18]	Valvular	Blood	Warm	Ante	55 (52)	65 ± 14 (66 ± 9)	56 (69)	CK-MB CPB time Cross-clamp time IABP use Mortality TnI
Vivacqua et al.[9]	Valvular	Blood	Cold	Ante	55 (55)	63 ± 13 (70 ± 11)	53 (64)	AF CPB time Cross-clamp time Inotropic support

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CK-MB, creatine kinase myocardial band; HTK, histidine–tryptophan–ketoglutarate; IABP, intra-aortic balloon pump; MDC, cardiopulmonary bypass; NR, not reported; TnI, troponin I.

pediatric cases; one study was excluded as it had a mixed population; and, three studies were excluded because they did not use HTK (-Figure S1). Seven studies were included in our analysis.[12–18]

2.6 | Outcomes

The primary outcomes analyzed were 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 (TnI).

2.7 | Risk of bias (quality) assessment

The risk of bias was assessed using a modified Jadad scale for randomized controlled trials.[19] Publication bias was investigated using funnel plots.[20]

2.8 | Data synthesis

Odds ratios (OR) were calculated for dichotomous data. Continuous data were compared using mean differences (MD; CPB duration, cross-clamp duration, TnI) and standardized mean difference (SMD; CK-MB). Where necessary medians and interquartile ranges were converted into means and *SD*s using the method of Hozo et al.[21] All analyses were conducted using Comprehensive Meta-Analysis (CMA) version 3. Heterogeneity was quantified using the Cochrane Q test[22] and all comparisons were made using random effects. We used a 5% level of significance and 95% confidence intervals (CIs); figures were produced using CMA. Ideally, the results of all trials carried out to investigate the effects of HTK in comparison to other types of cardioplegia would be published. Unfortunately, in reality, not all trials are published which may lead to selective reporting or publication bias. This can be detected in a funnel plot that is asymmetrical.

3 | RESULTS

The seven studies[9,12–18] included in the analysis had an aggregate of 804 participants, 412 of whom were HTK patients versus 391 who received MDC. The characteristics of the included studies are summarized in Table 1. The excluded RCTs and reasons for exclusion are listed in Table S1. The results are summarized with perioperative comparisons leading, followed by intraoperative variables and finally cardiac biomarkers. A summary of all the results can be seen in Table 2.

3.1 | CPB time

Seven studies involving 444 patients had their CPB duration measured (Figure 1). The overall MD was 2.103 min with 95% CI of −2.329 and 6.536; $p = .352$. Heterogeneity (I^2) was 77.7% and $p < .001$. There was, therefore, no overall significant difference in CPB time between HTK and other cardioplegias in our population. Subgroup analysis for CABG (HTK, $n = 165$; MDC, $n = 150$) had an MD of 8.291 min, with 95% CI of 0.033 and 16.549; $p = .049$; $I^2 = 30\%$ and $p = .255$. In this analysis, CPB time was shorter for MDC. Subgroup analysis for valvular population (HTK, $n = 179$; MDC, $n = 124$) had an MD of −0.401 min, with 95% CI of −5.655, 4.853; $p = .881$; $I^2 = 85.3\%$ and $p < .001$. There was, therefore, no significant difference in CPB time between HTK and MDC in the valvular population.

3.2 | Aortic cross-clamp time

Seven studies involving 668 patients measured the aortic cross-clamp duration (Figure 2). The overall MD was 0.276 min, with 95% CI of −2.569 and 3.120; $p = .849$; $I^2 = 60.4\%$ and $p = .019$. There was, therefore, no significant difference in aortic cross-clamp time between HTK and other cardioplegias in our population. Subgroup analysis for the CABG population (HTK, $n = 165$; MDC, $n = 150$) had an MD of 1.852 min, 95% CI of −4.34, 8.044; $p = .558$; $I^2 = 65.1\%$ and $p = .057$. There was, therefore, no significant difference in aortic cross-clamp time between HTK and MDC in the CABG population. Subgroup analysis for the valvular population (HTK, $n = 179$; MDC, $n = 124$) had an MD of −0.146 min, 95% CI of −3.348, 3.056; $p = .929$; $I^2 = 66.4\%$ and $p = .03$. There was, therefore, no significant difference in aortic cross-clamp time between HTK and MDC for the valvular population.

3.3 | Spontaneous defibrillation (spontaneous return of heartbeat)

Two studies involving 286 patients were measured for the incidence of spontaneous defibrillation (Figure 3). The OR for the comparison was 2.809, with 95% CI of 1.574, 5.012; $p < .001$; $I^2 = 0\%$ and $p = .754$. Spontaneous defibrillation, therefore, significantly favored HTK over MDC.

3.4 | Inotropic support

Four studies involving 306 patients measured the incidence for postoperative inotropic support (Figure 4). The OR was 1.5, with 95% CI of 0.742, 3.032; $p = .259$; $I^2 = 44.5\%$ and $p = .145$. There was therefore no significant difference in the use of inotropes between HTK and MDC. Subgroup analysis for the CABG population (HTK, $n = 80$; MDC, $n = 80$) had an OR of 0.616, 95% CI of 0.048, 7.965; $p = .24$; $I^2 = 27.5\%$ and $p = .24$. There was, therefore, no significant difference in the incidence of inotropic support between HTK and MDC in the CABG population. Subgroup analysis for the valvular population (HTK, $n = 93$; MDC, $n = 93$) had an OR of 1.613, 95% CI of 0.776, 3.354; $p = .20$; $I^2 = 37.9$ and $p = .204$. There was, therefore, no significant difference in the incidence of inotropic support between HTK and MDC in the valvular population.

3.5 | Mortality

Three studies involving 285 patients reported the incidence of mortality (Figure 5). The OR was 1.237, with 95% CI of 0.385, 3.978; $p = .721$; $I^2 = 0\%$ and $p = .605$. There was, therefore, no significant difference in the incidence of mortality between HTK and MDC.

3.6 | AF

Four studies involving 306 patients reported the incidence of postoperative AF (Figure 6). The OR was 0.809, with 95% CI of 0.511, 1.281; $p = .366$; $I^2 = 13.9\%$ and $p = .323$. There was, therefore,

TABLE 2 Summary of results

CPB time						
	Effect size	Lower limit	Upper limit	*p* value	I^2 (%)	*p* value for heterogeneity
Group						
CABG	MD = 8.291 min	0.033	16.549	.049	30	.255
Valve	MD = −0.401 min	−5.655	4.853	.881	85.3	.001
Overall	MD = 2.103 min	−2.329	6.536	.352	77.7	.001
Aortic cross-clamp time						
CABG	MD = 1.852 min	−4.34	8.044	.558	65.1	.057
Valve	MD = −0.146 min	−3.348	3.056	.929	66.4	.03
Overall	MD = 0.276 min	−2.569	3.120	.849	60.4	.019
Spontaneous return of heartbeat						
Overall	OR = 2.809	1.574	5.012	<.001	0	.754
Inotropic support						
CABG	OR = 0.616	0.048	7.965	.71	27.5	.24
Valve	OR = 1.613	0.776	3.354	.2	37.9	.204
Overall	OR = 1.5	0.742	3.032	.259	44.5	.145
Mortality						
Overall	OR = 1.237	0.385	3.978	.721	0	.605
Incidence of atrial fibrillation						
CABG	OR = 1.188	0.615	2.294	.608	0	.684
Valve	OR = 0.562	0.296	1.067	.078	0	.948
Overall	OR = 0.809	0.511	1.281	.366	13.9	.323
CK-MB						
CABG	SMD = 0.009	−0.267	0.286	.947	0	.521
Valve	SMD = −0.153	−0.538	0.231	.435	41.7	.19
Overall	SMD = −0.046	−0.27	0.178	.687	0	.44
Tn I						
Overall	MD = −1.424 ng/ml	−7.747	4.898	.659	78.4	.01

Abbreviations: CABG, coronary artery bypass graft; CK-MB, creatine kinase myocardial band; lower limit, lower 95% confidence interval; MD, mean difference; OR, odds ratio; SMD, standardized mean difference; TnI, troponin I; upper limit, upper 95% confidence interval.

no significant difference in the incidence of postoperative AF in either the HTK or other cardioplegia groups in our population. A subgroup analysis of the CABG population (HTK, $n = 80$; MDC, $n = 80$) had an OR of 1.188, 95% CI of 0.615, 2.294; $p = .608$; $I^2 = 0\%$ and $p = .684$. There was, therefore, no significant difference in the incidence of postoperative AF between HTK and MDC in the CABG population. Subgroup analysis for the valvular population (HTK, $n = 93$; MDC, $n = 93$) had an OR of 0.562, 95% CI of 0.296, 1.067; $p = .078$; $I^2 = 0\%$ and $p = .948$. There was, therefore, no significant difference in the incidence of postoperative AF between HTK and MDC in the valvular population.

3.7 | Release of CK-MB

Five studies involving 335 patients measured postoperative serum CK-MB concentrations (Figure 7). The SMD was −0.046, with 95% CI of −0.27, 0.178; $p = .687$; $I^2 = 0\%$ and $p = .44$. There was, therefore, no significant difference in serum CK-MB between HTK and MDC. Subgroup analysis for the CABG population (HTK, $n = 101$; MDC, $n = 101$) had an SMD of 0.009, with 95% CI of −0.267, 0.286; $p = .947$; $I^2 = 0\%$ and $p = .521$. There was, therefore, no significant difference in the serum CK-MB release between HTK and MDC in the CABG population. A subgroup analysis for the valvular population (HTK, $n = 93$; MDC, $n = 90$) had an SMD of −0.153, with 95% CI of −0.538, 0.231; $p = .435$; $I^2 = 41.7\%$ and $p = .19$. There was, therefore, no significant difference in the plasma CK-MB release between HTK and MDC in the valvular population.

3.8 | Release of TnI

Three studies involving 285 patients measured the postoperative serum TnI concentration (Figure 8). The MD was −1.424 ng/ml, with 95% CI of −7.747, 4.898; $p = .659$; $I^2 = 78.4\%$ and $p = .01$. There was, therefore,

Group by Surgery	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
CABG	Arslan et al (2005)	1.500	-9.954	12.954	0.257	0.797
CABG	Beyersdorf et al (1990)	7.000	-12.485	26.485	0.704	0.481
CABG	Gallandat Huet et al (1998)	13.800	4.636	22.964	2.951	0.003
CABG		8.291	0.033	16.549	1.968	0.049
Valve	Braathen et al (2011)	4.000	2.410	5.590	4.932	0.000
Valve	Gaudino et al (2013)	-3.000	-5.759	-0.241	-2.131	0.033
Valve	Kammerer et al (2012)	-2.000	-13.707	9.707	-0.335	0.738
Valve	Vivacqua et al (2019)	-3.000	-11.511	5.511	-0.691	0.490
Valve		-0.401	-5.655	4.853	-0.150	0.881
Overall		2.103	-2.329	6.536	0.930	0.352

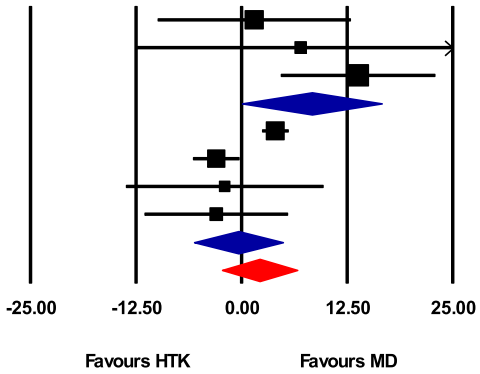

FIGURE 1 CPB time. On the left is a table displaying the mean difference, lower limit, upper limit, *z* value, and *p* value for each of the pooled studies with the final line presenting the overall statistics. On the right is a forest plot, which displays the mean difference (squares) and 95% CIs (whiskers) for each of the individual studies. Also shown is the overall mean difference (diamond) where the width of the diamond represents the 95% CIs. For the sake of clarity, the overall results with heterogeneity scores have been written below the forest plot. CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CI, confidence interval; HTK, histidine–tryptophan–ketoglutarate cardioplegia; MD, multidose cardioplegia

Group by Surgery	Study name	Difference in means	Lower limit	Upper limit	Z-Value	p-Value
CABG	Arslan et al (2005)	-2.300	-8.271	3.671	-0.755	0.450
CABG	Beyersdorf et al (1990)	0.000	-8.002	8.002	0.000	1.000
CABG	Gallandat Huet et al (1988)	7.100	1.781	12.419	2.616	0.009
CABG		1.852	-4.340	8.044	0.586	0.558
Valve	Braathen et al (2011)	2.000	0.651	3.349	2.906	0.004
Valve	Gaudino et al (2013)	-2.000	-4.565	0.565	-1.528	0.126
Valve	Kammerer et al (2012)	5.000	-12.098	22.098	0.573	0.567
Valve	Vivacqua et al (2019)	-3.000	-9.738	3.738	-0.873	0.383
Valve		-0.146	-3.348	3.056	-0.089	0.929
Overall		0.276	-2.569	3.120	0.190	0.849

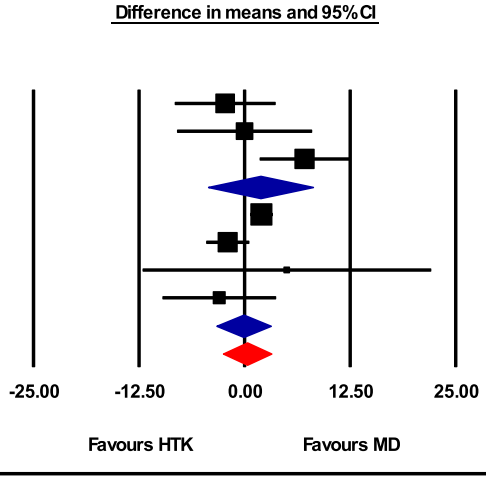

FIGURE 2 Cross-clamp time. All details as in Figure 1

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Beyersdorf et al (1990)	6.000	1.018	35.374	1.979	0.048
Gallandat Huet et al (1990)	2.566	1.390	4.735	3.015	0.003
	2.809	1.574	5.012	3.496	0.000

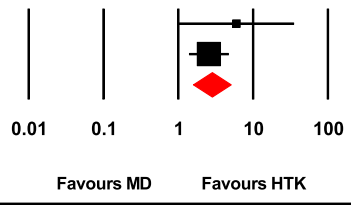

FIGURE 3 Spontaneous return of heartbeat. All details as in Figure 1, except that the effect size shown is the odds ratio

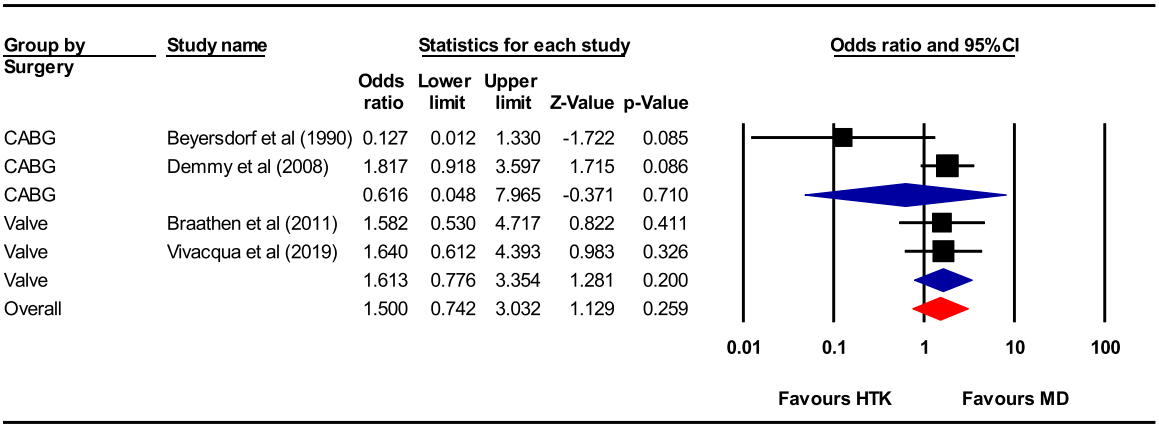

FIGURE 4 Inotropic support. All details as in Figure 3

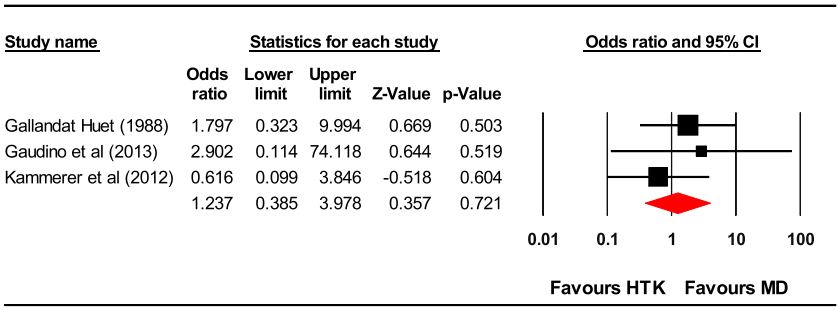

FIGURE 5 Mortality. All details as in Figure 3

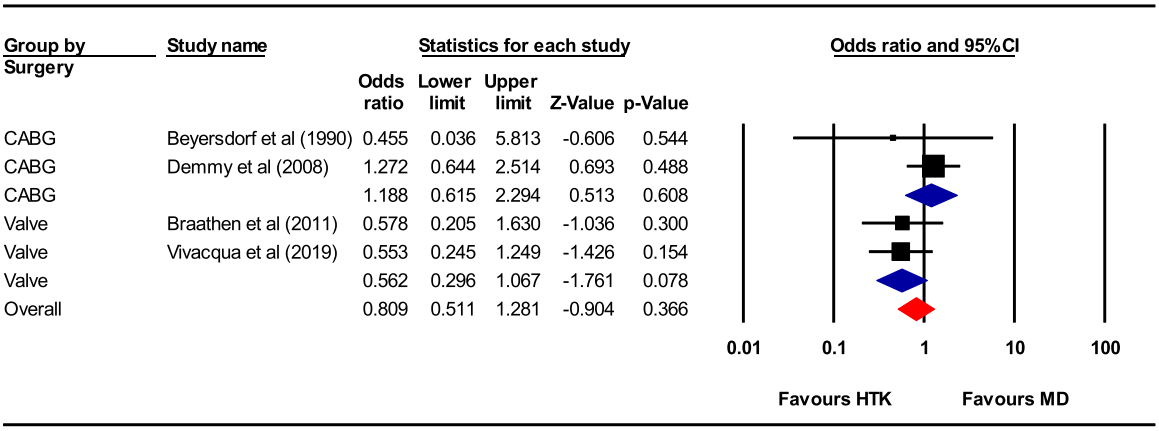

FIGURE 6 Incidence of atrial fibrillation. All details as in Figure 3

no significant difference in the serum TnI release between HTK and MDC.

3.9 | Study quality

The modified Jadad scale was used to assess study quality. The median score was 4 indicating studies were of moderate quality. None of the studies performed blinding and only one of the studies used an intention to treat analysis. On the positive side, no studies had incomplete data and all groups were matched at baseline. It was not possible to carry out subgroup analysis based on the quality of the studies as there was insufficient spread on either side of the median score.

4 | DISCUSSION

Cardioplegia has evolved since the inception of cardiac surgery itself. The current state of the industry sees several cardioplegia products presented to surgeons; with data often focussed only on areas of

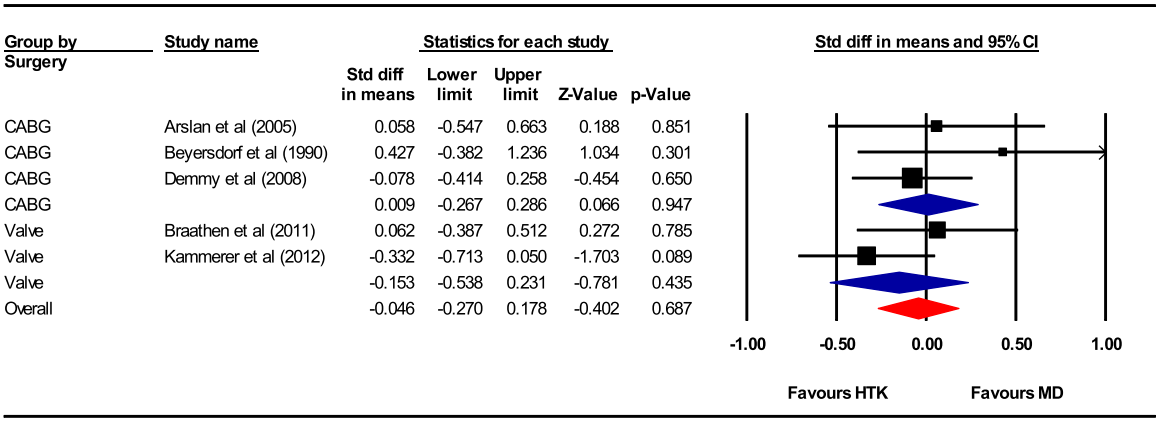

FIGURE 7 Creatine kinase myocardial band. All details as in Figure 1, except that the effect size shown is the standardized mean difference

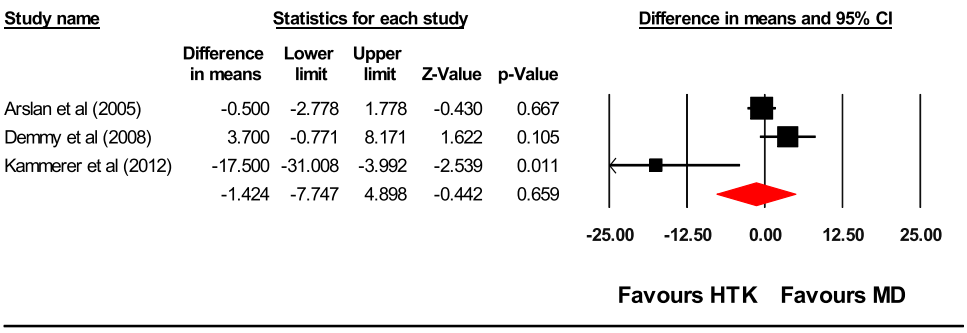

FIGURE 8 Troponin I. All details as in Figure 1

clear statistical advantage, with the present data of HTK in cardiac transplantation exemplifying this.[5] The lack of data presented by industry on the performance of HTK in the broader cardiothoracic arena, however, suggests that a review of the current literature is required to establish a fair consensus on the value of HTK in all cardiac surgery, with particular emphasis in this paper on the treatment of acquired pathology in adults. By producing this meta-analysis, we met our objective to determine whether superiority exists in HTK compared with other marketed cardioplegias in the adult population, with pooled data for several outcomes in both perioperative and postoperative phases, clinical and basic sciences; we have produced several parameters by which we can contribute to the discussion of HTK's role in cardiac surgery.

While major adverse cardiac and cerebrovascular events were rare (with stroke being a never event in our population), mortality was reported in both investigation groups. The statistical insignificance between cardioplegia groups for mortality suggest the cause of death in each case was unrelated to the chosen cardioplegia, with authors attributing preoperative ventricular impairment,[15] postoperative low cardiac output syndrome,[16] graft thrombosis,[14] and subsequent continued infarction[13] as the cause of death in their respective populations. Previous research suggests that neither cardioplegia type nor technique are significantly influential on the incidence of myocardial ischemia following surgery,[23] and this would, therefore, support our population authors' death attributions and the statistical findings of our pooled data.

The incidence of spontaneous defibrillation was shown to significantly favor the HTK group in our population. This analysis was derived from a moderate population size, and may suggest that HTK has greater protective qualities to the myocardium during aortic cross-clamp phase.

The incidence of postoperative administration of inotropes and postoperative AF also suggests the protective effect of cardioplegia on myocardial physiology and cardiomyocyte biochemistry. Our findings found insignificant differences between HTK and MDC for both parameters, suggesting that adverse events are due to other factors (such as perioperative myocardial handling, or cardioplegia technique)[24] rather than cardioplegia type. This is supported by our pooling of biochemical data, which found insignificant differences in TnI and CK-MB, suggesting that, while both were observed to be elevated in each study following surgery, there was no significantly greater concentration in either the HTK or multidose populations. The combination of pooled clinical and biochemical findings shows that, while myocardial physiology and biochemistry are disrupted perioperatively, these cases are sporadic and cannot be attributed to cardioplegia type in our population.

Duration of perioperative phases of surgery has been widely demonstrated to influence convalescence following surgery, for

example, the incidence of stroke.[25] CPB duration, during which patient blood is exposed to foreign surfaces via the CPB machinery, has correlated with several coagulopathic and pro-inflammatory responses within the body.[26] Statistically, retrospective surgical data analysis presents an issue of bias when measuring CPB duration. Surgeon bias, whereby cases with a greater anticipated duration are assigned single-dose cardioplegias (such as HTK, or del Nido cardioplegia) instead of multidose (i.e., blood or other crystalloid), often results in a statistically significant difference being found in CPB duration, favouring multidose solutions.[11,13] As a result of this observation, we selected randomized, prospective trials only, to ensure that any statistical difference in CPB duration would be the result of cardioplegia, and not procedure. Through this approach, we determined no statistically significant difference in either overall CPB duration, or indeed in the aortic cross-clamp duration. A commonly cited advantage of HTK is its single-dose administration,[4] and with our insignificant findings in perioperative phase durations, it is reasonable to suggest that surgeons opt for HTK when performing cases of complexity or extensive duration, owing to the lack of inconvenience bestowed by readministration of this cardioplegia.

We originally hypothesized that statistically significant differences in our clinical endpoints may be found by stratifying our data according to aortic cross-clamp duration, that is, ischemic time of >90 min versus ischemic time of <90 min. However, screening of participating literature revealed, at present, only one RCT[18] ($n = 107$) with mean cross-clamp duration of >90 min, which alone would render statistically meaningless data. Surgical data analysis relies on regular publication from individual centers; greater clarity will be derived on our cross-clamp duration hypothesis following the publication of further RCT data.

In a recent meta-analysis, Gambardella et al.[7] reported that del Nido cardioplegia was significantly favored in several of the outcomes investigated including spontaneous defibrillation. In contrast, our meta-analysis was solely focused on HTK cardioplegia in comparison to MDC and has shown that spontaneous defibrillation is higher in the HTK group. This and other limitations in Gambardella et al.,[7] as described in Section 1, suggest that it is too soon to be referring to superiority.

4.1 | Limitations

There was insufficient data to stratify clinical parameters according to cross-clamp duration time. It was hypothesized that statistical significance may exist in our clinical endpoints, should the data be stratified according to studies with a mean cross-clamp duration >90 min. However, only one study in our population met this criterion, and therefore, a meaningful analysis could not be performed.

4.2 | Conclusions

HTK and MDC are safe and effective in the myocardial protection of adult patients undergoing cardiac surgery. HTK was shown to be as effective as multidose in most clinical parameters measured.

Spontaneous defibrillation occurred significantly more often in the HTK group following aortic cross-clamp removal. More data measuring this parameter are needed to determine the external validity of this finding.

Single-dose administration of HTK is, therefore, the only significant difference in our population. Surgeon preference, anticipated procedure duration, and case complexity should therefore determine the selection of HTK when planning procedures.

More data are currently needed for procedures with a cross-clamp duration >90 min, to ascertain whether statistical significance exists between HTK and MDC in procedures over 90 min.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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