Systematic Review

Custodiol for myocardial protection and preservation: a systematic review

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Introduction: Custodiol cardioplegia is attractive for minimally invasive cardiac surgery, as a single dose provides a long period of myocardial protection. Despite widespread use in Europe, there is little data confirming its efficacy compared with conventional (blood or crystalloid) cardioplegia. There is similar enthusiasm for its use in organ preservation for transplant, but also a lack of data. This systematic review aimed to assess the evidence for the efficacy of Custodiol in myocardial protection and as a preservation solution in heart transplant.

Methods: Electronic searches were performed of six databases from inception to October 2013. Reviewers independently identified studies that compared Custodiol with conventional cardioplegia (blood or extracellular crystalloid) in adult patients for meta-analysis; large case series that reported results using Custodiol were analyzed. Next, we identified studies that compared Custodiol with other organ preservation solutions for organ preservation in heart transplant.

Results: Fourteen studies compared Custodiol with conventional cardioplegia for myocardial protection in adult cardiac surgery. No difference was identified in mortality; there was a trend for increased incidence of ventricular fibrillation in the Custodiol group that did not reach statistical significance. No difference was identified in studies that compared Custodiol with other solutions for heart transplant.

Conclusions: Despite widespread clinical use, the evidence supporting the superiority of Custodiol over other solutions for myocardial protection or organ preservation is limited. Large randomised trials are required.

Keywords: Custodiol solution; histidine-tryptophan-ketoglutarate solution; heart arrest; induced; cardiac transplantation

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Introduction

Custodiol is an intracellular crystalloid cardioplegic solution used by some centres for myocardial protection in complex cardiac surgery and for organ preservation in transplant surgery. Histidine-tryptophan-ketoglutarate (HTK), Bretschneider's, or Custodiol is attractive for cardiac surgeons because it is administered as a single dose and is claimed to offer myocardial protection for a period of up to three hours (1,2), allowing performance of complex procedures without interruption.

HTK was described by Bretschneider in the 1970s (3). It is classified as an intracellular, crystalloid cardioplegia due

Table 1 Custodiol ingredients [adapted from Viana *et al.* (5)]

Formulation ingredient	Value
Na^+	15 mmol/L
K^+	9 mmol/l
Mg^{2+}	4 mmol/L
Ca^{2+}	0.015 mmol/L
Histidine	198 mmol/L
Tryptophan	2 mmol/L
Ketoglutarate	1 mmol/L
Mannitol	30 mmol/L
pH	7.02-1.20

to its low sodium and calcium content. Sodium depletion of the extracellular space causes a hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. This is a different mechanism of action from conventional 'extracellular' cardioplegic solutions, which are high in potassium content and cause arrest by membrane depolarisation (4). The components of Custodiol are listed in *Table 1*. A high histidine content buffers the acidosis caused by the accumulation of anaerobic metabolites during the long ischaemic period; ketoglutarate improves ATP production during reperfusion; tryptophan stabilises the cell membrane and mannitol decreases cellular oedema and acts as a free-radical scavenger (2).

Despite its widespread use in Europe, there is very little data comparing the efficacy of Custodiol with conventional blood or crystalloid cardioplegia. There is also a paucity of data comparing Custodiol with other solutions for preservation of the heart in transplantation. There is concern about the adequacy of myocardial protection offered by only a single dose of cardioplegia. Similarly, concerns have been raised about hyponatraemia that follows the rapid administration of the requisite high volume of this low sodium cardioplegic solution (6,7).

Whilst initially introduced for myocardial protection in routine cardiac surgery, Custodiol has expanded into the field of transplantation. It has been used not only in cardiac transplantation, and adopted widely in Europe (8), but also in the preservation of multiple organs (9). Despite widespread use, its role in cardiac transplantation is as yet unclear. This is at least partially the result of the wide and expanding range of cardioplegia solutions that are used globally. A single review identified 167 different solutions in clinical use in the USA (10). There is a lack of high-quality randomised trials examining the influence of the cardioplegia solution on graft injury and early graft performance.

In this systematic review we performed a meta-analysis of outcomes related to myocardial protection reported by all studies comparing Custodiol with conventional cardioplegia (either blood or extracellular crystalloid). We reviewed results of large case series using Custodiol cardioplegia. Finally, we reviewed studies comparing Custodiol with other solutions used for organ preservation in heart transplantation.

Methods

Search methods for identification of studies

Electronic searches were performed of Ovid MEDLINE, Pubmed, EMBASE, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from inception to October 2013. The search strategy used a combination of 'histidine-tryptophan-ketoglutarate' or 'Bretschneider', or 'Custodiol' or 'cardioplegic solutions' or 'cardiac arrest (induced)' as keywords, MeSH and Emtree headings. Manual searches of reference lists were used to identify any studies not found in the initial search.

An extensive literature search was also performed to identify any additional large case series that used Custodial in their methods section, but was not listed in their title/abstract or MeSH/Emtree headings during the systematic search.

Selection criteria

Studies of both cardioplegia and cardiac transplantation in humans were identified. Those studies that reported the primary or secondary endpoints described in the research protocol, including mortality, myocardial protection and peri-operative morbidity, were included (11). Only studies in English language were considered for inclusion. The article types of abstract and letter were excluded. Inclusion was assessed by three independent reviewers (J.E., M.S. and B.D.), and differences of opinion were resolved by discussion with a senior investigator (J.P., M.P.V. and T.D.Y.).

Study end-points

The primary end-point for this study was mortality at

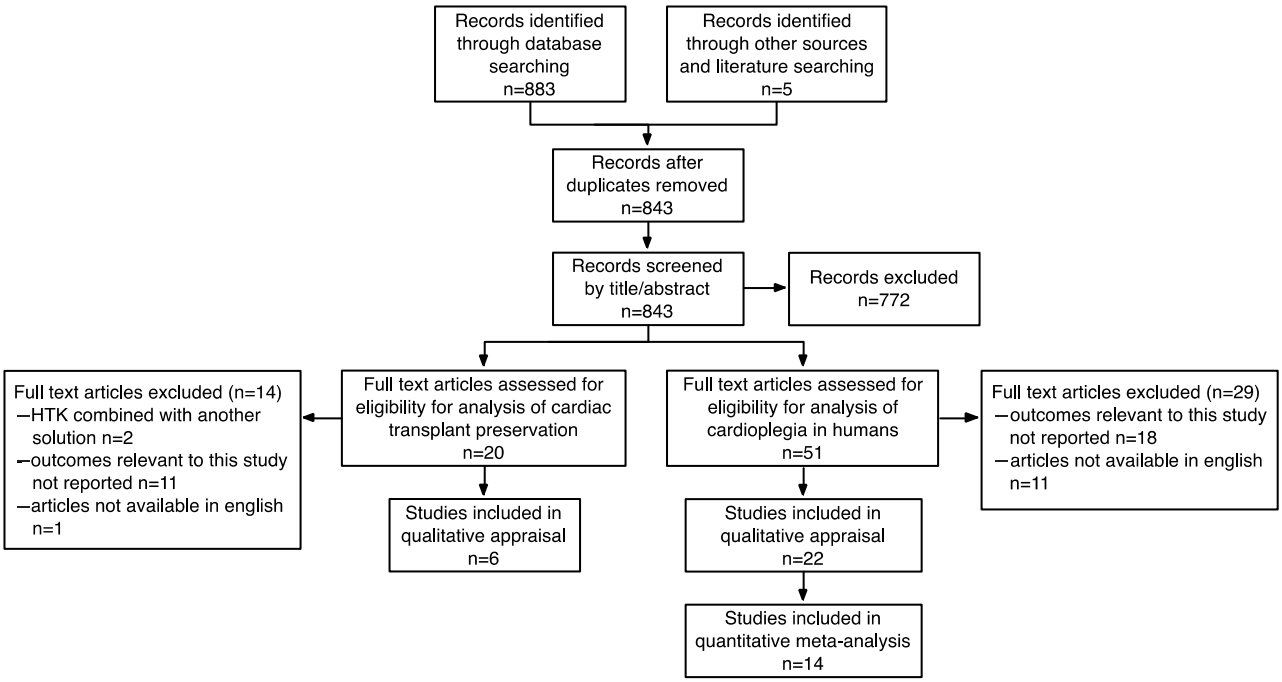

Figure 1 PRISMA diagram—search strategy, inclusion and exclusion of relevant studies.

30 days. Secondary endpoints included surrogates for myocardial protection [myocardial infarction, 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)].

Definitions

Myocardial infarction (MI) was defined as any two of the following: cardiac enzyme increase, new regional wall motion abnormality on echocardiogram or new Q-waves on electrocardiogram. We combined use of inotropes and LCOS as a single end-point. Criteria for inotrope use and a definition of LCOS were given by only two studies that reported these as end-points (12,13). Use of inotropes was in most studies at the treating clinician's discretion.

Statistical analysis

For the meta-analysis, the relative risk/risk ratio (RR) was used as a summary statistic. Both fixed and random effect models were tested: when there were variations between studies, a random effect model was used as the calculated ratios have a more conservative value. Heterogeneity was tested using χ^2 tests. If there was a substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. Continuous variables were analyzed using inverse variance with the calculation of mean difference as the summary statistic in both fixed and random effects models, as above.

Results

Search results

The systematic search identified 51 potentially relevant cardioplegia studies and 20 potentially relevant cardiac transplantation studies. Reasons for exclusion are detailed in the flow-diagram in *Figure 1*, according to the PRISMA statement (14).

Twenty-two cardioplegia studies satisfied the inclusion criteria for qualitative appraisal. Fourteen comparative studies were further selected for quantitative meta-analysis and eight large case-series were examined for qualitative appraisal. Two studies, comparing Custodiol to intermittent aortic clamping and perfused VF were not included in meta-analysis because they were not comparable to other studies using conventional cardioplegia (15,16).

Six cardiac transplantation studies satisfied inclusion

criteria and were included in a qualitative review.

Meta-analysis of studies comparing Custodiol to conventional cardioplegia

Patients and demographics

Table 2 shows details of 14 comparative studies included in the meta-analysis. Twelve of the 14 studies sought primarily to determine the outcomes related to Custodiol cardioplegia and compared similar surgical procedures. The primary aim of two studies was to determine efficacy of a particular surgical technique that happened to use Custodiol as cardioplegia (19,23).

Primary endpoint—mortality

Nine studies reported mortality (5,11,18-20,23,25-27). Overall, the 925 patients receiving Custodiol had a similar risk of mortality as the 911 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, 0.59-1.88, P=0.86; *Figure 2*). There was no significant heterogeneity between the studies (I^2=0%; heterogeneity P=0.55). Including studies where only similar surgical procedures were compared, there remained no difference in the rate of mortality (RR 0.89, 95% CI, 0.40-1.96, P=0.77, n=766).

Secondary endpoints

Myocardial protection

Five studies reported the rate of peri-procedural MI as per the definition listed in the methods (5,12,13,21,23). The rate of MI reported in the 677 patients given Custodiol did not differ from 677 patients receiving conventional cardioplegia (Custodiol 2.81% *vs.* 1.62%, RR 1.72, 95% CI, 0.82-3.60, P=0.15). There was no heterogeneity between studies (I^2=0%, heterogeneity P=0.53).

Five studies reported mean creatine kinase (CK-MB) or troponin-I (Tn-I) (12,18,21,22,26). In these studies, there was a trend towards shorter cross-clamp time in the conventional cardioplegia groups (weighted mean: Custodiol 62.9 min *vs.* conventional 54.8 min, P=0.11). Mean differences for both CK-MB and TnI did not differ between groups (CK-MB: mean difference –4.15 (–12.41-4.10), P=0.32, *Figure 3*; Tn-I: mean difference 0.90, 95% CI, –4.68-6.48, P=0.75).

Seven studies reported the need for inotropes or a low cardiac output syndrome in the immediate post-operative period, and included a total of 1,408 patients (12,13,17,20,21,23,26). The rate of inotropes/Low cardiac output syndrome (LCOS) did not differ between groups (Custodiol 15.0% *vs.* conventional 12.7%, RR 1.33, 95% CI, 0.86-2.05, P=0.20). Heterogeneity of the results between studies limits interpretation of the result (I^2=64%, heterogeneity P=0.01). Only one study (13) reported significantly lower incidence of inotropic support in the Custodiol group. The reason for this heterogeneity in results was not immediately clear on review of the methodology. Three studies reported the use of mechanical support, with no significant difference between groups (5,21,27).

Arrhythmia

Eight studies reported the incidence of ventricular arrhythmias during reperfusion (Custodiol n=710, conventional n=715) (12,13,17,18,20,23,24,26). Six of the eight studies that reported a higher incidence of VF after removal of the cross clamp in the Custodiol group. Overall, there was a trend for increased incidence that reached statistical significance in the fixed but not the random effects model (Custodiol 20.1% *vs.* 9.7%, random effects RR 1.84, 95% CI, 0.91-3.74, P=0.09, *Figure 4*; fixed effects: RR 2.12, 95% CI, 1.63-2.76, P<0.001). Only two studies reported a lower rate of VF after Custodiol (13,24) and this resulted in significant heterogeneity between studies (I^2=80%, heterogeneity P<0.001). The reason for the difference in results reported by these studies was not immediately clear on qualitative review.

Four studies (336 patients) reported the incidence of AF in the post-operative period (12,20,21,23). There was no significant difference in the rate of AF between groups (Custodiol 34.3% *vs.* conventional 17.7%, RR 1.36, 95% CI, 0.74-2.50, P=0.32). Only one study reported a significantly greater incidence of AF in patients given Custodiol, which contributed to the significant heterogeneity in the analysis (I^2=87%, heterogeneity P<0.001).

Qualitative appraisal of large case-series of Custodiol cardioplegia

Case series of any adult cardiac surgery were included if they reported results of >100 patients and exclusively used Custodiol cardioplegia. Eight series satisfied these criteria, reporting the results from a total of 6,840 patients (28-35). The details of these studies are in *Table 3*. Mortality was the only outcome universally reported. The rates of mortality reported in these studies are similar to other series reporting

Table 2 Comparative study details

Study	Institution	Study type	Study period	Conventional cardioplegia type	N (conventional)	N (HTK)	Surgery type (conventional)	Surgery type (HTK)	Cross-clamp time [conventional]
Gaudino *et al*. 2013 (17)	Catholic University, Rome, Italy	RCT	01/2007-08/2008	Warm blood	29	31	Mitral valve surgery (sternotomy)	Mitral valve surgery (sternotomy)	74.0
Viana *et al*. 2013 (5)	Austin Hospital, Melbourne, Australia	PM	01/2005-01/2011	Blood	71	71	CABG 70%, Valve 38%, Dissection 2%	CABG 33%, Valve 86%, Dissection 11%	145 [33]
Kammerer *et al*. 2012 (18)	Academic Teachin Hospital, Ludwigshafen, Germany	RCT	07/2008-09/2009	Warm blood (Calafiore)	52	55	MIMS	MIMS	72.1 [27.2]
Sansone *et al*. 2012 (19)	Mauriziano Umberto I Hospital, Turin, Italy	C	Sternotomy 02/ 2005-10/2008 Right mini 10/ 2008-05/2010	Blood	50	50	AVR (sternotomy)	AVR (right mini-thoracotomy)	44.8±13.4
Braathen *et al*. 2011 (12)	Oslo University Hospital, Oslo, Norway	RCT	03/2007-12/2009	Cold blood	38	38	Mitral valve surgery	Mitral valve surgery	73 [3]
Scrascia *et al*. 2011 (20)	University of Bari, Bari, Italy	C	01/2003-03/2008	Cold blood	58	54	Thoracic aortic surgery	Thoracic aortic surgery	126 [61]
Demmy *et al*. 2008 (21)	Multi-institutional (USA/Canada)	RCT		Plegisol	68	68	CABG	CABG	37±10
Arslan *et al*. 2005 (22)	Baskent University, Ankara, Turkey	RCT		Extracellular crystalloid	21	21	CABG	CABG	36.2±11.3
Wiesenack *et al*. 2004 (23)	University Hospital Regensberg, Regensberg, Germany	C	01/2000–02/2004	Warm blood	485	485	CABG (miniature circuit),	CABG (standard circuit)	48±15
Careaga *et al*. 2001 (13)	Hospital de Cardiologia, Mexico City, Mexico	RCT	01/2000–09/2000	Cold crystalloid	15	15	CABG 5 (33%), Valve 7 (47%), Congenital 2 (13%)	CABG 6 (40%), Valve 7 (47%), Congenital 2 (13%)	66.6
Sakata *et al*. 1998 (24)	Sapporo Medical University School of Medicine, Sapporo, Japan	C	01/1994–12/1996	Cold blood	26	20	Mitral valve surgery	Mitral valve surgery	106±27
Hachida *et al*. 1997 (25)	The Heart Institute of Japan, Tokyo, Japan	C	01/1981–10/1994	Insulin/ glucose/ potassium	11	9	Aortic valve/aortic surgery (all dilated ventricles), XC>200 min	Aortic valve/aortic surgery (all dilated ventricles) XC>200 min	234.5±10.8
Beyersdorf *et al*. 1990 (26)	J.W Goethe University, Frankfurt	RCT		Blood	12	12	Mitral surgery via sternotomy	Mitral surgery via sternotomy	51±23
Gallandat Huet *et al*. 1988 (27)	University Hospital Groningen, Groningen, Netherlands	RCT	02/1986–11/1986	St Thomas	117	132	CABG	CABG	52.9±19.1

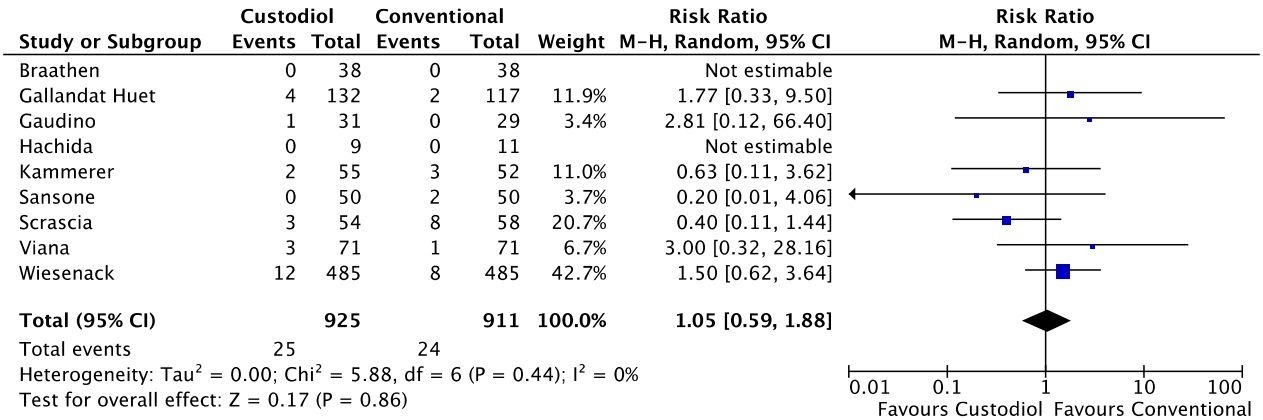

Figure 2 Mortality: Custodiol versus conventional cardioplegia for myocardial protection. CI, confidence interval; M-H, Mantel-Haenszel.

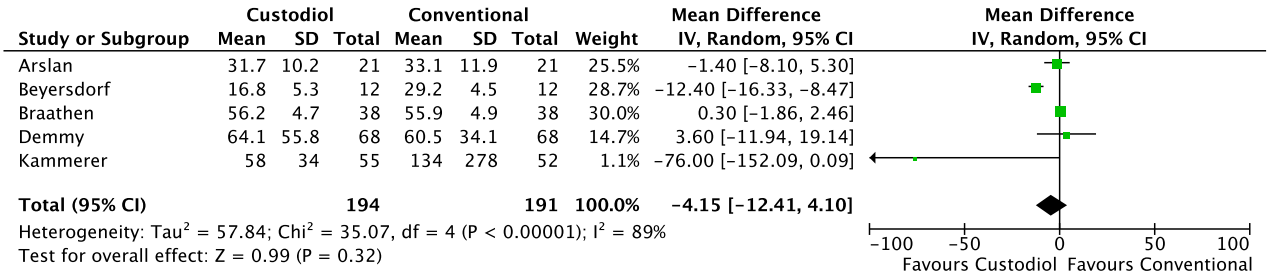

Figure 3 CK-MB: Custodiol versus conventional cardioplegia for myocardial protection. CI, confidence interval; IV, inverse variance; SD, standard deviation.

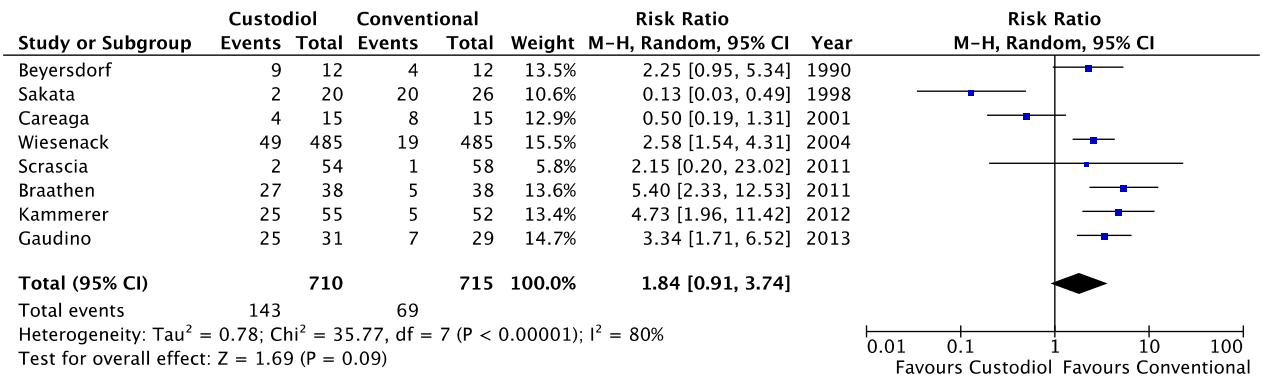

Figure 4 Ventricular fibrillation: Custodiol versus conventional cardioplegia for myocardial protection.

similar surgical procedures using conventional cardioplegia.

Custodiol for cardiac transplantation

Three studies were identified comparing Custodiol with other solutions for heart preservation in transplant (36-38). There were three case series, one of which duplicated results reported from one of the comparative studies (8,39,40). Mortality was reported by five studies, acute graft failure or rejection by three (*Table 4*).

There is only one randomised study comparing Custodiol with other solutions for preservation in heart

Table 3 Large case series using Custodiol for myocardial protection

Study	Period	Institution	Type	Surgery	N	Age	Mortality
Di Eusanio *et al*. 2013 (28)	01/2007-07/2012	Orsola-Malpighi Hospital, Bologna, Italy	Case series	Frozen elephant trunk aortic surgery	122	61±10	17.2%
Shrestha *et al*. 2013 (32)	03/1982-03/2012	Hanover Medical School, Hanover, Germany	Case series	Total arch replacement with elephant trunk (39% acute dissection; 31% redo)	179	56.4±12.6	Intra-op 1.7%; 30 days 17.3%
Misfeld and Davierwala, 2012 (30)	1999-2012	Heart Centre, Leipzig	Case series	Mitral Valve Replacement via right mini-thoracotomy	2,731		1.2%
Shrestha *et al*. 2012 (31)	07/1993-12/2000	Hanover Medical School, Hanover, Germany	Case series	David valve-sparing aortic root repair	126	57 [8-83]	4.8%
Martin *et al*. 2008 (33)	09/2005-06/2006	German Heart Centre, Munich, Germany	Case series	All cardiac (with CPB), Coronary Artery Bypass Graft (CABG) 43%, Valve 28%, Aprotinin *vs*. tranexamic acid (TXA)	1,188`	66.4	4.1%
Salvador *et al*. 2008 (34)	1986-2006	Santa Maria dei Battuti Hospital, Treviso, Italy	Case series	Mitral valve repair	608	55±11	1%
Weis *et al*. 2006 (35)	01/2002-12/2003	University of Munich, Munich, Germany	Case series	All valve, CABG and combined	1,558	66.3 y	2.2%
Minami *et al*. 2005 (29)	02/1985-04/2004	Heart Centre North Rhine, Bad Oeynhausen, Germany	Case series	Aortic Valve Replacement	1,516	77.1% <80 y	6.6% 30 day

Table 4 Transplant heart preservation

Study	Year	Type	Comparator	Age HTK	Age Other	N histidine-tryptophan-ketoglutarate (HTK)	N Other	Mortality HTK	Mortality other	Acute graft failure HTK	Acute graft failure other
Cannata *et al*. 2012 (36)	01/2006-12/2010	Cohort	Celsior or St Thomas	47.7±12.7	48.6	61	72	10/61 (16.3%)	9/72 (12.5%)	14.7%	CS 10.5%, ST 14.7%
Kofler *et al*. 2009 (39)	1981-1994	Case series		45.2±11.9	46.3±15.2	222	118	65.3%	70.3%		
Garlicki *et al*. 2003 (37)		RCT	UW, Celsior	45±13.3	UW 40.6±12, CS 48.4±11.4	15	UW 17 CS 16			33.4%	UW 23.5%, CS 0%
Minami *et al*. 2003 (40)		Case series						6.1%			
Reichenspurner *et al*. 1994 (38)		Cohort	UW	46.2±6.9	47.5±7.8	159	50	24/159 (15%)	5/50 (10%)	3.7%	2.0%
Reichenspurner *et al*. 1993 (8)		Case series				600		15.5%		4.2%	

MVR, mitral valve replacement; CBP, cardiopulmonary bypass; CAGB, coronary artery graft bypass; TXA, tranexamic acid; AVR, aortic valve replacement; HTK, histidine-tryptophan-ketoglutarate; UW, University of Wisconsin; CS, Celsior; ST, St Thomas's.

transplant (37). Forty-eight cardiac transplants were randomised to Custodiol, UW or Celsior. Cardiac index was equivalent across all three groups. The Celsior group achieved spontaneous recovery of sinus rhythm more often that the Custodiol or UW groups. Unfortunately, no data on rates of acute graft dysfunction was provided as those with acute graft dysfunction were excluded. The group reported acute rejection (67% Custodiol, 47% UW, 19% Celsior) and rates of allograft vasculopathy as assessed by IVUS at one year (100% Custodiol, 88% UW, 69% Celsior). There was no difference in ischaemic time between groups but the authors argue that inferior myocardial protection and subsequent increase in inflammatory response may have been the mechanism causing the increased rate of acute rejection and later development of allograft vasculopathy.

Discussion

Debate continues as to the ideal cardioplegic solution for myocardial protection in cardiac surgery. A meta-analysis of randomised trials comparing intermittent blood and crystalloid cardioplegia concluded that blood offers superior myocardial protection, but none of the included studies used Custodiol in the crystalloid group (41). Similar debate continues as to the ideal solution for organ preservation in heart (and indeed other solid organ) transplantation.

Custodiol for myocardial protection

This systematic review included both randomised and non-randomised studies, comparing a total of 2,114 patients in meta-analysis and 6,840 patients in case series. The meta-analysis suggests no significant difference between Custodiol and conventional cardioplegia for the primary endpoint mortality, or the secondary endpoints used as surrogate markers of myocardial protection during cardiac surgery. The similar rate of mortality (in a comparison of 1,836 patients) and CK-MB, MI and LCOS/inotrope confirms the safety of the Custodiol in comparison to conventional cardioplegia.

Experimental animal models of cardioplegic arrest using Custodiol versus conventional cardioplegia have been critical of the myocardial protection offered by Custodiol. Fannelop and colleagues randomised 16 pigs placed on cardiopulmonary bypass (CPB) to cardioplegic arrest with a single dose of Custodiol or intermittent cold-blood cardioplegia (42). Pigs receiving Custodiol had lower cardiac indices, ventricular function and higher troponin-T release in the first four post-operative hours compared with pigs receiving cold-blood cardioplegia. A similar advantage for pigs randomised to intermittent St Thomas' Hospital Solution compared to single dose Custodiol was reported by Aarsaether and colleagues (43). These studies contrast with that of Chen and colleagues, who in neonatal piglets randomised to Custodiol or multi-dose blood cardioplegia for protection during a 2-hour cross-clamp time show equivalent myocardial protection by biochemical and histopathological assessment (44).

Studies comparing Custodiol with conventional intermittent cardioplegia in paediatric patients have reported conflicting results. In a retrospective study of neonates undergoing arterial switch operation, Bojan and colleagues reported a higher troponin release in those who received Custodiol compared with warm blood cardioplegia (45). In contrast, Korun and colleagues reported no significant difference in clinical outcomes of paediatric patients undergoing surgery for congenital heart disease (46). However, liver enzymes and an apoptosis index (measured from biopsies taken of the right ventricle) correlated with cross clamp time in the conventional cardioplegia group, but not the Custodiol group. A similar finding was made by Liu *et al.*, who reported lower mortality with use of Custodiol for cross clamp times >90 min when compared with conventional cardioplegia (47).

Right ventricular (RV) function after mitral valve surgery is an independent predictor of survival (48), thus its protection is of paramount importance. One small randomised study has questioned the adequacy of right ventricular myocardial protection offered by Custodiol compared with conventional cardioplegia (intermittent warm blood) (17). Patients with poor pre-operative RV function (as measured by tricuspid annular plane systolic excursion—TAPSE) randomised to myocardial protection with Custodiol had a lower RV ejection fraction and volumes, and worse clinical outcome (lower cardiac indices, higher pulmonary pressures, longer period of time on inotropes) in the post-operative period than those protected with whole blood cardioplegia. There was no difference in the outcome of those with normal pre-operative RV function protected with Custodiol versus intermittent blood (17).

The majority of comparative studies have reported an increased rate of VF as the first rhythm after reperfusion with Custodiol cardioplegia. The increased rate of ventricular arrhythmias after removal of cross-clamp in

the Custodiol group did not reach statistical significance, with evidence of heterogeneity in the included studies. The reason for this is not clear. Some authors have suggested that VF after reperfusion may be an indication of inadequate myocardial protection (47), but no studies have related an initial VF rhythm to adverse outcomes.

There is concern about the significant hyponatraemia and acidosis that results from rapid infusion of a large volume of Custodiol (Na^+ 15 mmol/L) (6,7). None of the comparative studies included in the meta-analysis reported serum sodium levels, nor any outcomes that might be considered surrogates of clinical hyponatraemia. Similarly, none of the series that report (or indeed investigate) hyponatraemia were large enough to satisfy inclusion criteria for this study. In a series of 25 patients, Lindner *et al*. measured serum sodium and osmolality at 11 intra- and post-operative time-points (49). Whilst patients had a significant (and rapid) decrease in serum sodium (15 mmol/L), there was no significant change in osmolality, suggesting an isotonic hyponatremia. Others have observed hyponatraemia without clinical consequence (5,50). Many groups treat hyponatremia after Custodiol administration with a haemofilter on the cardiopulmonary bypass circuit, or prevent it altogether by aspirating the antegrade-directed cardioplegia from a retrograde cannula (13).

Custodiol for cardiac transplantation

The human studies on Custodiol as a preservation solution for cardiac transplantation are few in number and are (except for one) non-randomised. A number of small animal studies suggest superiority of Custodiol over UW (51), Celsior (52,53) St. Thomas' solution and Krebs-Heinseleit Buffer (KHB) (54) with Custodiol-preserved hearts having better indices of left-ventricular function (51) and also demonstrating lower circulating levels of both TnI and CK, indicating less graft injury (52,53). There also appears to be better preservation of myocardial ATP stores (51-53) reduced markers of ischaemia-reperfusion injury as well as reduced apoptosis of myocardial cells (52,53). The mechanism by which Custodiol limits ischaemia/reperfusion injury in transplant is unclear, but may be due to the higher level of ATP-producing anaerobic glycolysis (53). One study has suggested that left ventricular function may be better preserved with Celsior cardioplegia (54), although the same paper demonstrated less myocardial oedema in Custodiol-preserved hearts.

There is, to date, only one large animal study comparing Custodiol to Celsior. This work was done with canine hearts and demonstrated that after 12 hours of ischaemia Custodiol-preserved hearts had significantly better left ventricular function, required less defibrillation in the reperfusion period to achieve sinus rhythm, were less prone to arrhythmic events once sinus rhythm was achieved and had a better myocardial ATP:ADP ratio (55).

Despite compelling evidence from small and large animal studies, solid data from human clinical trials supporting the use of Custodiol over other preservation solutions is lacking. The pre-clinical data is sufficient to encourage large-scale, quality randomised trials to answer the compelling question of which preservation solution provides optimal protection for the cardiac allograft.

Limitations

The limitations in this study reflect the relative paucity of data comparing Custodiol with conventional cardioplegia in adult cardiac surgery, and the need for a large randomised trial. The objective of two of the studies included in the meta-analysis was to compare different surgical techniques rather than the mode of cardioplegia. We were cognisant of the potential to introduce bias by including such studies but nevertheless did so due to the few studies specifically designed to investigate the efficacy of Custodiol. In these studies it is likely that surgical procedure significantly influenced the results. The majority of patients contributing to the MI and LCOS/inotrope analysis came from the study by Wiesenack *et al*. (23) This study concluded that the rate of MI and low cardiac output is lower by using a miniature cardiopulmonary bypass (CPB) circuit (with conventional cardioplegia) compared with a standard length CPB circuit (with Custodiol). Sansone *et al*. reported a trend towards lower mortality in patients undergoing minimally invasive aortic valve surgery (using Custodiol) compared with AVR via sternotomy (with blood cardioplegia) (19). This limits the conclusions that can be made by this review. A clinical trial comparing Custodiol with cold blood cardioplegia (NCT01681095) is currently recruiting patients (target 110 patients) undergoing cardiovascular surgery.

Conclusions

The results of the available evidence suggest that Custodiol offers myocardial protection that is equivalent to that of conventional cardioplegia. However, the body of evidence available from which to draw conclusions is limited by

the small number of randomised patients. A single dose cardioplegia strategy for myocardial protection has significant benefits for the performance of minimally invasive or complex cardiac surgery and the results of this review support its ongoing use. However, there is not enough evidence to recommend the routine use of Custodiol for the performance of coronary artery bypass grafting (CABG) or other simple open cardiac surgical procedures. There is not enough evidence from human studies to assess the efficacy of Custodiol for organ preservation. Large, randomised trials are required to determine the efficacy of Custodiol for both myocardial protection in cardiac surgery and myocardial preservation in cardiac transplant.

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