CUSTODIOL®
HTK Solution
The Clear Choice

HEART & ORGAN PRESERVATION SOLUTION

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Introduction to Custodiol® HTK Solution

Custodiol® HTK Solution is intended for perfusion and flushing of the heart (as well as donor liver, kidney and pancreas) prior to removal from the donor for preserving the heart during hypothermic storage and transport to the recipient. It is based on the principal of inactivating organ function by withdrawal of extracellular sodium and calcium, together with intense buffering of the extracellular space by means of histidine/histidine HCl, so as to prolong the period for which the organs will tolerate interruption of blood and oxygen.

Advantages of Custodiol® HTK Solution include:

- Improved survival rate and graft function.[1]
- Single dose of Bretschneider's HTK solution could effectively reduce pumping time and afford similar myocardial protection compared with repeated doses of cold blood cardioplegia (CBC) in the preservation of donated hearts.[2]
- Contains lower concentrations of sodium, calcium and potassium and induces cardiac arrest by deprivation of extra-cellular sodium for action potential.[2]
- Ketoglutarate provides high energy production via adenosine triphosphate during reperfusion and tryptophan stabilizes cell membranes.
- Mannitol acts in osmotic regulation of the cell membrane.
- The major advantages of Custodiol HTK solution are derived from histidine, which acts as a buffer, enhancing the efficiency of anaerobic glycolysis. Kresh et al. found that a histidine protein-type buffer solution was superior to bicarbonate-based and tromethamine based hyperkalmic crystalloid cardioplegic solutions for stabilizing intracellular pH and postoperative biochemical and mechanical data.[3]

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A Comparison in Donor Heart Preservation: A Comparison between Custodiol Histidine-Tryptophan-Ketoglutarate (HTK) Solution and Celsior

A recent single center retrospective study compared Custodiol vs Celsior solution in short-term outcomes in heart transplant.[1]

The authors concluded that Custodiol was superior in heart preservation when compared to Celsior. BMI>/= 35 and Celsior are the risk factors at short term survival.[1]

With a population of 223 heart transplants, the author found out that the survival rate (91.2% Custodiol vs 78.5% Celsior) and graft function (91.2% Custodiol vs 74.4% Celsior) were superior when Custodiol was used as preservation solution.

Custodiol HTK vs Celsior in Short-term Outcomes		
Variable	**Adjusted HR (95% CI)**	**p Value**
Celsior (versus HTK)	4.69 (1.01, 21.73)	0.048
Age (years)	1.02 (0.96, 1.08)	0.50
BMI ≥ 35	10.63 (1.79, 63.2)	0.01
White	3 (0.56, 16.21)	0.20
CMV Status, D+/R-	0.33 (0.04, 2.6)	0.29
Total Bilirubin	1.5 (0.7, 3.21)	0.30
Coronary Artery Disease	0.32 (0.08, 1.3)	0.11
C statistic = 0.81; BIC = 1515 30-day survival, Cox proportional hazards model (N = 223)		

Comparison of the Most Commonly Used Cardioplegia				
Patient Outcome, Overall				**0.01**
Alive	188 (84.3%)	93 (91.2%)	95 (78.5%)	
Dead	35 (15.7%)	9 (8.8%)	26 (21.5%)	
Graft Outcome, Overall				**0.001**
Functioning	183 (82.1%)	93 (91.2%)	90 (74.4%)	
Failure	40 (17.9%)	9 (8.8%)	31 (25.6%)	

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A Comparison in Donor Heart Preservation: A Comparison between Bretschneider's Histidine-Tryptophan-Ketoglutarate (HTK) Solution and Cold Blood Cardioplegia

This study aimed to compare the efficacy of myocardial protection using single dose of Bretschneider's histidine-tryptophan-ketoglutarate (HTK) solution and repeated doses of cold blood cardioplegia (CBC) in donor heart preservation for heart transplant.[2]

The authors concluded that a single dose of Custodiol HTK solution or repeated doses of CBC solution afford similar myocardial protection in the preservation of donated hearts.[2]

Multivariate analysis shows the significant reduced pumping time in HTK group (p = .002)

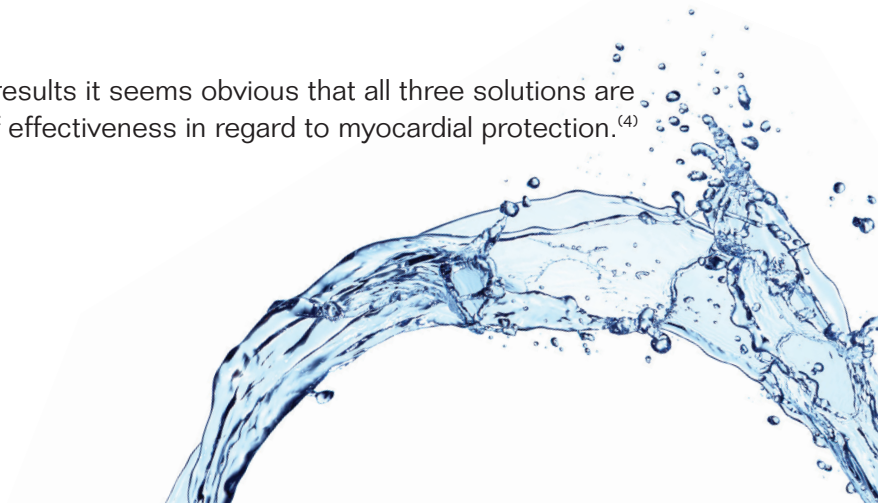
Clinical Variable	HTK (n = 16)	STH (n = 45)	p Value
Inotropic score at 24 h postoperatively	19.4 ± 15.5	7.1 ± 6.3	<.001
Pumping Time (min) .002	158.3 ± 32.0	173.9 ± 33.2	.002
LIVEF (%) at 7 d Postoperatively	62.0 ± 4.4	60.7 ± 7.3	.806
Age (y)	50.7 ± 11.5	50.6 ± 12.5	.648

Multivariate Analysis of Surviving Patients
Data are shown as mean ± standard deviation.
Abbreviations: LVEF, left ventricular ejection fraction; HTK, histidine tryptophan ketoglutarate solution; STH, St Thomas' Hospital solution

Myocardial Protection for Transplantation[4]

The present study is a randomized clinical trial assessing preservation of the donor heart using three common cardioplegic solutions. (Table1, opposite page)[4]

Based on collected results it seems obvious that all three solutions are in the same range of effectiveness in regard to myocardial protection.[4]



Composition of UW, HTK and Celsior Solutions			
Substrates (mmol/L)	**UW**	**HTK**	**Celsior**
Lactobionate	100	-	80
Raffinose	30	-	-
NA+	30	15	-
K+	125	10	-
MG++	5	4	-
Cl-	-	50	-
H2P04-	25	-	-
SO4-	5	-	-
Adenosine	5	-	-
Allopurinal	1	-	-
Glutathione	3	-	3
Insulin	100	-	-
Dexamethasone	8	-	-
HES	50	-	-
Bactrim ml/L	0.5	-	-
Osmolarity	320	310	320
PH(O st. C)	7.4	7.2	7.3
Mannitol	-	30	60
Glutamate	-	-	20
CaCl2	-	0.015	0.245
NAOH	-	-	100
KCl	-	9	15
MgCl2	-	4	13
Histidine	-	198	30
Tryptophan	-	2	-
Ketoglutarate	-	1	-

Mortality	2 Days		14 Days		90 Days		Summary	
Solution	n	%	n	%	n	%	n	%
Celsior	1	4.0	3	11	4	14	4	14
HTK	6	5.0	17	12	17	12	17	12
UW	3	4.0	9	13	11	16	11	17

Mortality in the 224 Recipients

In our study, histologic changes in the zero biopsies analysis of donor data, total ischemic time, reperfusion time, mortality rate, and hemodynamic parameters indicated that HTK cardioplegia is more optimal in our conditions. [4]

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HTK Solution Compared to UW for Cardiac Transplantation[5]

The purpose of this study was to assess the efficacy of Custodiol HTK solution as compared with UW solution in experimental heart preservation.[5]

This table shows the recovery of hemodynamic data on the heart for 8 and 12 hours of preservation. Following 8 hours of preservation the recovery of AF, CF, CO, SP and RPP in HTK group (2) was significantly increased compared with that in group 1 ($p<.05$)[5]

	Time				
Group	**(h)**	**CO**	**AF**	**CF**	**RPP**
1. UW (n = 7)	8	49.7 ± 2.4	47.4 ± 4.2	57.1 ± 6.2 7	1.0 ± 1.8
2. HTK (n = 8)	8	78.1 ± 5.9*	71.5 ± 8.6*	87.8 ± 5.8*	83.6 ± 4.4*
3. UW (n = 5)	12	16.6 ± 3.4	10.7 ± 2.4	37.6 ± 8.4	40.9 ± 8.2
4. HTK (n = 5)	12	29.7 ± 1.4#	24.2 ± 2.5#	4.26 ± 1.5	56.7 ± 4.1
Cardiac Functional Recovery (%) mean = SE*, <.05 vs. Group 1#, <.05 vs Group 3 CO; cardiac output, AF; aortic flow, CF; coronary flow ; RPP rate pressure product					

We found a better recovery of cardiac function and lower leakage of CPK in the hearts stored in HTK solution compared with those in UW solution following 8 hours of storage.[5]

The efficacy of HTK Solution is attributed to the high buffering capacity provided by the histidine, which suppresses ischemia-induced acidosis and sustains a cytosolic ATO level.

In conclusion, HTK solution is much more effective than UW solution for heart preservation. HTK may lead to better techniques of heart preservation for transplantation.[5]

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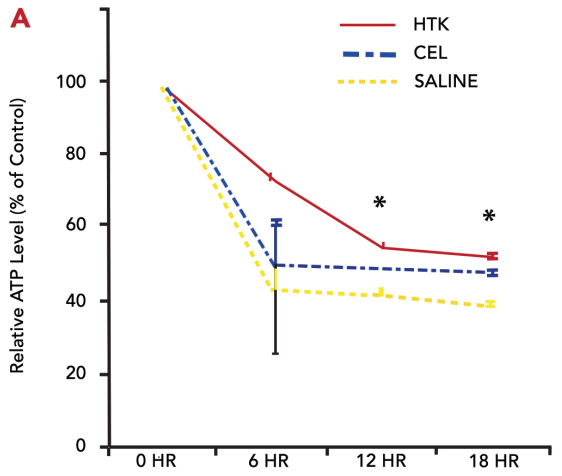
Efficacy of Protective Qualities HTK Solution[6]

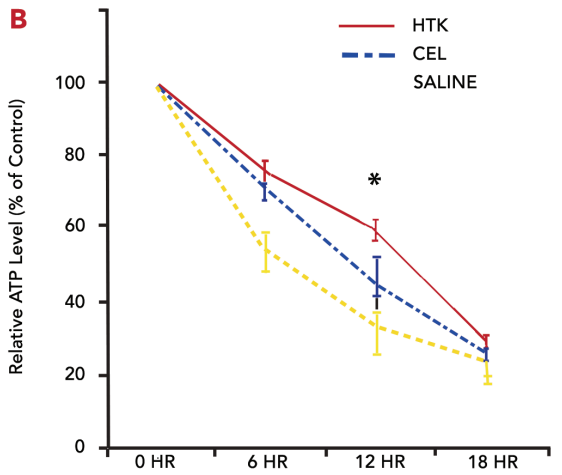
This study compared the protective effects of two widely used preservation solutions, histidine-tryptophan-ketoglutarate (HTK) and Celsior (CEL) for ischemia-reperfusion injury using a rat heterotopic heart transplantation model with older donors.[6]

The authors concluded that Custodiol HTK exhibits superior protections during cold storage in a syngenic rat heart transplantation model compared with CEL.[6]

HTK Solution Preserves ATP Levels in Cardiac Grafts[6]



HTK-Treated Grafts Have Less Metabolic Stress[6]



Myocardial Damage and Lipid Peroxidation From Hearts of Younger and Older Donors

Hearts From Younger Donors (n = 5)				
Markers	Saline	CEL	HTK	p Value[a]
Of myocardial damage				
Serum CPK	5,360.8 ±	2,336.6 ±	1,946.1 ±	0.402
(IU/l)	1,385.8	841.0	837.1	
Serum troponin I (pg/mL)	127.3 ± 37.5	37.4 ± 18.5	40.6 ± 20.1	0.312
Serum HMGB1 (ng/mL)	1.32 ± 0.62	1.15 ± 0.55	1.15 ± 0.21	0.462
Of oxidative damage				
Tissue MDA (umol/mg total protein)	1.38 ± 0.43	1.11 ± 0.14	1.00 ± 0.42	0.15

Hearts From Older Donors (n = 5)				
Markers	**Saline**	**CEL**	**HTK**	**p Value[a]**
Of myocardial damage				
Serum CPK	9,594.8 ±	8,094.1 ±	4,620.3 ±	0.048
(IU/l)	1,526.7	673.0	441.4a	
Serum troponin I (pg/mL)	304.1 ± 9.1	184.8 ± 33.0	141.7 ± 36.5a	0.0184
Serum HMGB1 (ng/mL)	3.17 ± 1.79	2.33 ± 0.52	0.98 ± 0.75a	0.0258
Of oxidative damage				
Tissue MDA (umol/mg total protein)	2.57 ± 0.84	1.34 ± 0.18	0.8 ± 0.13	0.0014

CEL = Celsior; CPK = creatine phosphokinase; HMGB1 = high-mobility group box 1; HTK = histidine-tryptophan-ketoglutarate; MDA = malondialdehyde.
aValues are means ± SD; p values vs CEL are shown.

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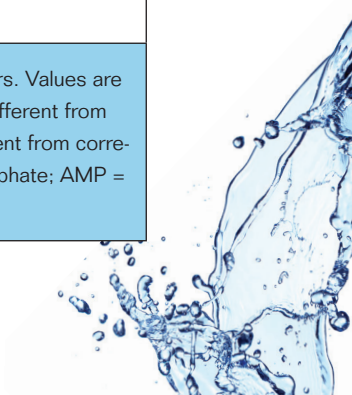
Custodiol® Versus Celsior®

The aim of this experimental study was to compare the protective efficacy of the cardioplegic solutions Celsior and Custodiol. Canine hearts were examined with regard to energy metabolism and early post-ischemic recovery after 8 or 12 hours of ischemia at 5°C.[7]

The authors concluded that, in the canine heart, Celsior showed no advantage over cardioplegia with Custodiol. Differences were observed however, which may be clinically important especially in the case of long storage times.

8 Hours Ischemia at 5°C		
	Custodiol®	**Celsior®**
Phosphocreatine	5.1 ± 0.3	4.0 ± 0.2[a]
ATP	20.1 ± 0.6	17.7 ± 1.3
ADP	6.4 ± 0.3	7.0 ± 0.3
AMP	1.4 ± 0.1	1.7 ± 0.1
ATP/ADP ratio	3.2 ± 0.2	2.5 ± 0.1b
Lactate	99.3 ± 3.7	81.5 ± 8.1[a]
Glycogen	142.3 ± 18.7	155.8 ±11.3
There was no significant difference in myocardial ATP content between preservation solutions after 8 hours. After 12 hours, hearts of the Custodiol group contained significantly more ATP compared with Celsior-treated hearts ($p < 0.05$). The ATP/ADP ratio was significantly higher in Custodiol-treated hearts after both ischemic times. ($p < 0.01$, 12 hours $p < 0.05$) [7]		

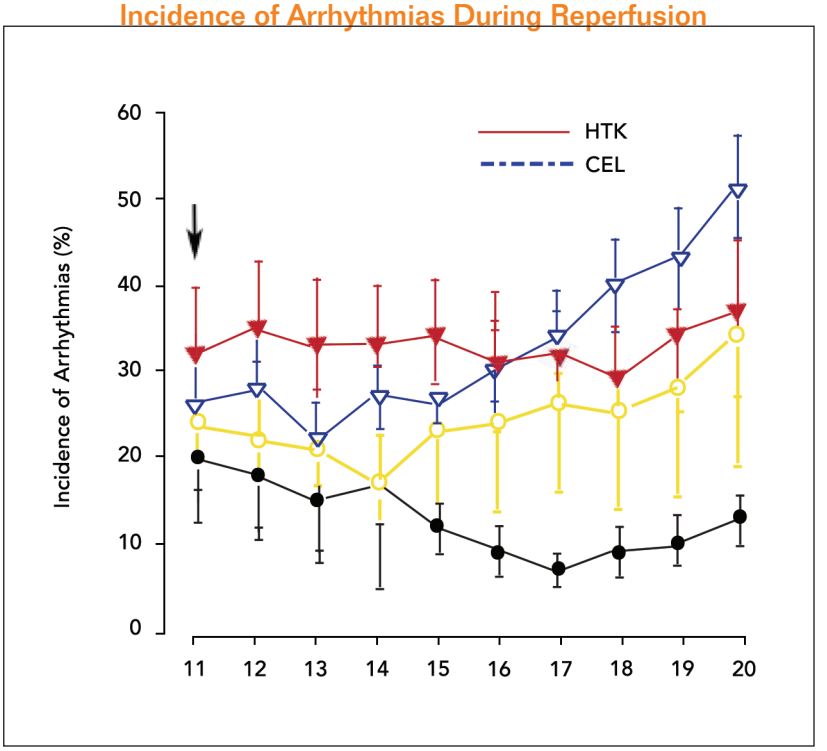
12 Hours Ischemia at 5°C		
	Custodiol®	**Celsior®**
Phosphocreatine	3.2 ± 0.5	2.4 ± 0.5
ATP	14.1 ± 0.6	11.3 ± 1.0
ADP	6.3 ± 0.3	6.9 ± 0.5
AMP	2.1 ± 0.3	2.4 ± 0.2
ATP/ADP ratio	2.3 ± 0.0	1.6 ± 0.1[a]
Lactate	134.4 ± 6.3	116.2 ± 11.3[a]
Glycogen	111.2 ± 16.8	119.6 ±23.8
Hearts were perfused with Custodiol or Celsior and stored at 5°C for 8 or 12 hours. Values are means ± SEM of five experiments (given as µmol/g dry weight). [a] Significantly different from corresponding ischemic time of the Custodiol group; $p < 0.05$. [b] Significantly different from corresponding ischemic time of the Custodiol group; $p < 0.01$.ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.		



Heart Arrhythmias

Comparing the incidence of arrhythmias during the first 20 minutes of reperfusion, Celsior-treated hearts showed a higher rate – arrhythmic beats than Custodiol-treated hearts after 8 hours as well as after 12 hours of ischemia. The difference was significant after 8 hours (ANOVA, $p < 0.01$) but not after 12 hours of ischemia.[7]

Incidence of Arrhythmias During Reperfusion



Hearts were perfused with Custodiol (—o—, —•—) or Celsior (—▼—, — —) and stored at 5°C for 8 hours (—•—, — ▼—[a]) or 12 hours (—o—, — —). Values are means ± SEM, n = 7 for each group.
[a]Significantly different from corresponding ischemic time of the Custodiol group; analysis of variance $p < 0.01$.

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About Essential Pharmaceuticals

Owned by Accord Healthcare, Inc., Essential Pharmaceuticals has served the needs of the medical community since 2006 and Custodiol® HTK has been used since 2000 throughout heart and organ preservation. Essential Pharmaceuticals has the exclusive sales and distribution rights to Custodiol® HTK in the United States and Canada.

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