A multicenter, randomized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts


Ann Thorac Surg 2001;71:1442-1447

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A Multicenter, Randomized, Controlled Trial of Celsior for Flush and Hypothermic Storage of Cardiac Allografts

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Background. A multicenter, randomized, controlled, open-label trial was conducted to evaluate the safety and efficacy of Celsior when used for flush and hypothermic storage of donor hearts before transplantation.

Methods. Heart transplant recipients were randomized to one of two treatment groups in which donor hearts were flushed and stored in either Celsior or conventional preservation solution(s) (control). Study subjects were followed for 30 days after transplantation.

Results. A total of 131 heart transplant recipients were enrolled (Celsior, n = 64; control, n = 67). The treatment groups were evenly distributed in donor and recipient base line characteristics. Graft loss rate was lower in the Celsior group on day 7 (3% versus 9%) and on day 30 (6% versus 13%), but the difference was not statistically significant based on 95% confidence interval analysis. No significant difference was measured between the Celsior and control groups in 7-day patient survival (97% versus 94%) and the proportion of patients with one or more adverse events (Celsior, 88%; control 87%) or serious adverse events (Celsior, 38%; control, 46%). Significantly fewer patients in the Celsior group developed at least one cardiac-related serious adverse event (13% versus 25%).

Conclusions. Celsior was demonstrated to be as safe and effective as conventional solutions for flush and cold storage of cardiac allografts before transplantation.


Cardiac transplantation has become a viable therapeutic option for patients with end-stage heart disease, regardless of etiology. Significant progress has been made over the last 30 years in donor management, operative technique, immunosuppression regimens, and postoperative critical care. Despite these advances, primary graft dysfunction and acute right heart failure are not uncommon complications after orthotopic cardiac transplantation and contribute substantially to postoperative morbidity and mortality. Although the etiology of these hemodynamic failures are multifactorial, undoubtedly suboptimal cardiac preservation and subsequent ischemia-reperfusion injury sustained by the cardiac allograft play a critical role [1]. As a result, efforts are ongoing to develop improved means of preservation. Advances in myocardial preservation may reduce postoperative inotropic agent requirements, decrease length of hospitalization, and allow the use of previously rejected marginal donor hearts. Furthermore, accepted ischemic times may be lengthened allowing time for prospective cross-matches and wider geographic distribution of donor hearts.

Topical hypothermia is one of the underlying principles of organ preservation in heart transplantation. Consensus on the optimal solution for flush and cold storage of cardiac allografts has not been established [2–4]. Based on historic and regional preference, a variety of preservation solutions, such as ViaSpan (DuPont Pharmaceutical, Wilmington, DE), Plegisol (St. Thomas) (Abbott Laboratories, Abbott Park, IL), and noncommercial solutions formulated and compounded locally are used by individual heart transplant centers [5–7]. In some centers,
the same solution is used for both flush and storage, whereas other centers have elected to use separate solutions for initial cardioplegia and subsequent cold storage and transport of the cardiac allograft. With these conventional preservation solutions, the maximum allowable storage time of cardiac allografts is approximately 6 hours.

Celsior (SangStat Medical Corporation, Fremont, CA) is a rationally designed solution for the flush and hypothermic storage of cardiac allografts. The purpose of this study was to evaluate the safety and efficacy of Celsior in comparison with conventional preservation solutions when used for flush and hypothermic storage of donor hearts before transplantation.

Material and Methods

Study Design

This multicenter, randomized, controlled, open-label study was conducted between May 1997 and May 1998. The study protocol was approved by the Institutional Review Boards of 18 heart transplant centers in the United States and Canada. Eligible subjects were enrolled from 17 study centers. This study was conducted in accordance with the provisions of the Declaration of Helsinki, in compliance with the requirements of the Institutional Review Board of each participating center, and according to Good Clinical Practice.

Informed consent was obtained from each participating subject. Patients who were eligible for participation in this study were recipients of primary cardiac allografts, were between 18 and 65 years of age, and had adequate renal function (serum creatinine less than 2.5 mg/dL). Significant exclusion criteria for the donor were abnormal donor coronary angiogram and donor-to-recipient body ratio of less than 0.6. Major exclusion criteria for the recipient included pretransplant pulmonary vascular resistance of more than 4.0 Wood units, prior organ transplants, ventilator dependence at the time of transplant, placement of a ventricular assist device within 30 days before transplant, current panel reactive antibody more than 20%, congenital heart disease, requirement of high intensity care in the intensive care unit.

When a suitable heart donor was identified for an eligible recipient, the recipient was randomly assigned to the Celsior group or the control group in a 1:1 ratio. In the Celsior group, the donor heart was flushed and stored with Celsior. In the control group, flush and cold storage of the donor heart was performed using a single solution or separate solutions. The conventional preservation solutions used in the control group were in accordance with local standard practice and was consistent within each individual participating transplant center. The flush or cold storage solutions used in the control group included ViaSpan, Roe cardioplegic solution, Ringers lactate, normal saline, Plasmalyte A, Plegisol, Carmichael's solution, Stanford solution, and various locally prepared, noncommercial solutions.

Donor hearts were procured using standard techniques. Diastolic arrest of the heart was accomplished with 1 L of cold (4° to 8°C) Celsior solution or control preservation solution. Topical hypothermia was achieved with saline slush. The preservation solution was administered according to the standard practice for each center, either before or after the donor heart was removed. Excluded hearts were then immersed in 1 to 2 L of either the Celsior solution or the control preservation solution at 4°C to 8°C. Preserved donor hearts were stored in closed cardiac storage containers under ice before transport to the recipient's location. Implantation was performed using standard surgical techniques at each center.

After transplantation, standard postoperative patient care practices for the individual study centers, including immunosuppressive protocols, were followed. Study subjects were followed for 30 days posttransplant.

The primary endpoint was 7-day patient survival. Secondary safety end points included 7-day graft survival, 30-day patient survival, 30-day graft survival, and the incidence of cardiac-related adverse events. Graft loss was defined as patient death, retransplantation, or requirement of mechanical ventricular support. Adverse events were recorded according to preferred terms and body systems using a COSTART dictionary [8]. Changes were made to the standard COSTART dictionary for adverse event terminology to refine the safety assessments for this study. Events included under the “cardiovascular” body system category were reviewed, and specific events were assigned to a separate “cardiac-related” category. The distinctions were made to separate those events strictly affecting the heart, and thus presumably more relevant to heart transplant patients, from other cardiovascular system events. In accordance with federal guidelines, a serious adverse event was defined as an event that was fatal, life-threatening, permanently disabling, a congenital anomaly, a cancer, an overdose, or one that required prolonged hospitalization. Acute allograft rejection was defined as a biopsy reading of grade 2 or greater based on the International Society for Heart and Lung Transplantation schema [9].

Efficacy end points were secondary in this study. Evaluated efficacy end points included time to cardiopulmonary bypass weaning, requirement for inotropic support, time to independent cardiac function, pacing requirements, electrocardiogram findings (day 7), ejection fraction (day 7), wall motion abnormality (day 7), time to sinus rhythm, hemodynamic status (intraoperative through 12 hours after transplant), duration of assisted ventilation, and duration of stay in the hospital and intensive care unit.

Statistical Analysis

The sample size was calculated to demonstrate equivalence in 30-day patient survival. Based on the assumption that the two treatment groups had an equivalent 30-day patient survival of 90%, it was estimated that 60 patients per group would be required to provide the study with more than 90% power to demonstrate that the Celsior group was a maximum of 20% less than the control group.
using a one-sided 95% confidence bound. The primary analysis of study results was based on intention to treat. No interim analyses of safety or efficacy were conducted.

Evaluation of the primary end point, 7-day patient survival, was performed using a one-sided 95% confidence interval approach. The two treatment groups were considered equivalent if the lower one-sided confidence bound for the (Celsior – control) difference in patient survival was more than 0.20. Analysis of 7-day graft survival, 30-day patient survival and graft survival, serious adverse events, and cardiac-related adverse events were also carried out using a one-sided 95% confidence interval.

Secondary analysis of efficacy end points was performed using two-sided 95% confidence intervals for the difference between the Celsior and control groups. All efficacy treatment comparisons were performed using the two-tailed procedure because the intent was to describe potential differences and not to determine equivalence or superiority.

Results

Between May 1997 and May 1998, 133 heart transplant recipients were enrolled from 17 cardiac transplant centers, including 65 patients in the Celsior group and 68 in the control group. One patient in each treatment arm did not receive a transplant following randomization. Transplantation was cancelled for 1 patient in the Celsior group because of the development of elevated pulmonary artery pressures in the recipient, and in 1 patient in the control group because of renal cell carcinoma in the donor. These 2 cases were excluded from further analysis, and the intent-to-treat analysis thus included 64 patients in the Celsior group and 67 patients in the control group.

Table 1. Base Line Donor and Recipient Characteristics of 131 Heart Transplant Recipients Enrolled and Randomized to the Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Celsior (n = 64)</th>
<th>Control (n = 67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age (years)</td>
<td>30 ± 14</td>
<td>33 ± 12</td>
<td>0.178</td>
</tr>
<tr>
<td>(range 12–63)</td>
<td>(range 12–58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor race: white</td>
<td>47 (73%)</td>
<td>61 (91%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Donor required inotropic support with dopamine &gt; 10 μg/kg per minute</td>
<td>6 (13%)</td>
<td>12 (23%)</td>
<td>0.613</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>53 ± 9</td>
<td>49 ± 11</td>
<td>0.027</td>
</tr>
<tr>
<td>(range 21–68)</td>
<td>(range 22–68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient gender: Female</td>
<td>9 (14%)</td>
<td>14 (21%)</td>
<td>0.417</td>
</tr>
<tr>
<td>Recipient CMV positive</td>
<td>40 (63%)</td>
<td>44 (66%)</td>
<td>0.822</td>
</tr>
<tr>
<td>Recipient blood type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type O</td>
<td>29 (45%)</td>
<td>24 (36%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Type A</td>
<td>21 (33%)</td>
<td>36 (54%)</td>
<td></td>
</tr>
<tr>
<td>Duration of recipient hospitalization before transplant (days)</td>
<td>66 ± 62</td>
<td>50 ± 44</td>
<td>0.121</td>
</tr>
<tr>
<td>Cause of recipient’s end-stage heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>31 (48%)</td>
<td>40 (60%)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>25 (39%)</td>
<td>19 (28%)</td>
<td></td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>0.576</td>
</tr>
<tr>
<td>Other</td>
<td>6 (9%)</td>
<td>6 (9%)</td>
<td></td>
</tr>
<tr>
<td>Positive T-cell crossmatch (retrospective)</td>
<td>6 (9%)</td>
<td>2 (3%)</td>
<td>0.353</td>
</tr>
<tr>
<td>Total HLA mismatches (A, B, DR)</td>
<td>4.4 ± 1.4</td>
<td>4.6 ± 1.2</td>
<td>0.560</td>
</tr>
<tr>
<td>Total ischemic time (hours)</td>
<td>3.3 ± 1.0</td>
<td>3.1 ± 1.0</td>
<td>0.328</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD for continuous variables, and as n (%) for categorical variables.

CMV = cytomegalovirus; HLA = human lymphocyte antigen.

Base line characteristics of the donors and recipients are shown in Table 1. As expected, most recipients were middle-aged, male, and white. The two study groups were evenly distributed in base line donor and recipient characteristics. Statistically significant differences between the two groups included a higher percentage of white donors in the control group, older recipients in the Celsior group, and fewer patients with type A blood in the Celsior group. These differences in base line characteristics were not clinically significant.

The two study groups were evenly distributed in procurement procedures and in the total volume of Celsior or conventional solutions required during procurement. Three donor hearts in the Celsior group were flushed with Celsior but were stored in saline. These 3 cases were included in the intent-to-treat analysis.

Patient and Graft Survival Rates

The 7- and 30-day patient and graft survival rates are presented in Table 2. Patient survival on day 7 posttransplant (primary end point) was excellent in both groups and did not differ. Fewer patients in the Celsior group had graft loss in the first 7 days after transplantation than in the control group (3% versus 9%), but the difference did not reach statistical significance. Of the 6 patients in the control group who had graft loss in the first 7 days, 2 patients survived but required retransplantation or prolonged mechanical circulatory support. By day 30 posttransplant, graft loss occurred in 6% of patients in the Celsior group compared with 13% in the control group, although the difference did not reach statistical signifi-
cance. Of the 9 patients who had graft loss in the control group, 1 patient underwent retransplantation.

Adverse Events

Adverse events are summarized by body system in Figure 1. There was no statistically significant difference between the study groups in the proportion of patients who experienced one or more adverse events during the study (Celsior, 88%; control, 87%). There were also no notable differences between treatment groups with regard to the incidence of any adverse event. As expected, most adverse events were attributed to the cardiac system. Overall, the proportion of patients experiencing potentially drug-related (ie, possibly, probably, or definitely drug-related) adverse events was low (Celsior, 13%; control, 10%). When evaluated by severity, 36% (n = 23) of the Celsior group experienced a severe adverse event compared with 33% (n = 22) of the control group. Fewer patients in the Celsior group (38%) experienced at least one serious adverse event compared with the control group (46%), but this difference was not statistically significant (one-sided 95% upper bound for the difference = 5.4).

A total of 12 deaths occurred in this study: 4 (6%) in the Celsior group and 8 (12%) in the control group, a difference that was not significantly different. The causes of death are shown in Table 3. One death in each treatment group was considered possibly related to inadequate myocardial preservation. These included 1 death resulting from right ventricular dysfunction in the Celsior group and 1 death from right heart failure in the control group. Of the 4 deaths in the Celsior group, 1 (25%) was cardiac-related, whereas in the control group 5 of the 8 deaths (63%) were cardiac-related.

The most common adverse events in the cardiac system are shown in Figure 2. Most cardiac-related adverse events were acute allograft rejection, cardiovascular disorder (such as left ventricular dysfunction, right ventricular dysfunction, nonspecific graft dysfunction, and mitral regurgitation), and atrial fibrillation. There was no difference in the proportion of patients who had one or more cardiac-related adverse event (Celsior, 66%; control, 69%) in the study. However, fewer patients in the Celsior group experienced at least one cardiac-related serious adverse event (13%) compared with the control group (25%). Because the one-sided upper confidence bound for the difference (Celsior – control) was −1.8, this difference was statistically significant.

Acute Allograft Rejection and Infections

Endomyocardial biopsy was performed in accordance with standard practice in each participating transplant center, mostly for routine surveillance. No difference was found in the incidence of acute allograft rejection between the two groups; acute rejection was detected in

Table 2. Patient and Graft Survival After Transplant in Cardiac Transplant Recipients Randomized to the Celsior or Control Group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Patient survival, n (%)</th>
<th>Graft survival, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-day</td>
<td>30-day</td>
</tr>
<tr>
<td>Celsior (n = 64)</td>
<td>62 (97%)</td>
<td>60 (94%)</td>
</tr>
<tr>
<td>Control (n = 67)</td>
<td>63 (94%)</td>
<td>59 (88%)</td>
</tr>
</tbody>
</table>

Lower one-sided 95% confidence bound for Celsior – Control, patient survival: at 7 days = −3.1, at 30 days = −2.5; graft survival: at 7 days = −0.9, at 30 days = −1.3. No difference is statistically significant.

Table 3. Causes of Death in 4 Patients Randomized to the Celsior Group and 8 Patients Randomized to the Control Group

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Celsior</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular dysfunction (1)</td>
<td>Cardiogenic shock (4)</td>
<td></td>
</tr>
<tr>
<td>Sepsis (1)</td>
<td>Pneumonia (1)</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (1)</td>
<td>Acute rejection (1)</td>
<td></td>
</tr>
<tr>
<td>Cause unknown (1)</td>
<td>Right heart failure (1)</td>
<td></td>
</tr>
<tr>
<td>Cardiac tamponade (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of patients are in parentheses.

Fig 1. Incidence of adverse events occurring in more than 5% of patients in either treatment group, by body system. There was no difference between the treatment groups in any adverse event.
31% of the Celsior patients and 37% of control patients. There was also no difference between the study groups in the proportion of patients who developed at least one infection (Celsior, 36%; control, 28%).

**Efficacy**

No statistically significant differences were found between the two study groups in any efficacy end point. The duration of cardiopulmonary bypass was similar between treatment groups (Celsior, 2.5 ± 0.7 hours; control, 2.4 ± 0.9 hours). A similar proportion of patients had cardiopulmonary bypass reinstated after weaning (Celsior, 8%; control, 9%). All concomitant medications used within 30 days after transplantation were recorded. There was no difference in requirements of pharmacologic agents, such as dobutamine, dopamine, milrinone, norepinephrine, isoproterenol, thryoxine, triidoothyronine, or phenylephrine in the posttransplant period.

There were no differences between groups in electrocardiogram results on day 7. Normal sinus rhythm or sinus tachycardia was detected in 87% of patients in the Celsior group and in 89% of patients in the control group. Among patients who had allograft function assessed using echocardiogram or multigated angiogram, mean ejection fraction was comparable between the Celsior group (0.60 ± 0.07) and the control group (0.59 ± 0.07). Similarly, wall motion abnormalities other than septal hypokinesis were detected in a similar proportion of patients between the Celsior group (none) and the control group (8%).

The treatment groups were similar with respect to mean duration of assisted ventilation (32 ± 47 hours for the Celsior group and 31 ± 49 hours for the control group). Likewise, the proportion of patients requiring assisted ventilation for more than 24 hours was similar between the groups (Celsior, 31%; control, 34%). The treatment groups had similar time to independent cardiac function, defined as the time from release of recipient aorta cross-clamp to termination of all intravenous inotropic, chronotropic, and vasodilator agents after transplantation (Celsior, 155 ± 123 hours; control, 154 ± 95 hours). The time to sinus rhythm (Celsior, 9 ± 39 hours; control, 6 ± 35 hours) was similar in both study groups. Ten to 18 hours after admission to the intensive care unit, mean heart rate was 115 ± 19 beats per minute in the Celsior patients and 113 ± 16 beats per minute in the control patients, and normal sinus rhythm or sinus tachycardia was observed in 81% of the Celsior patients and in 80% of the control patients. There was no significant difference between the two groups in the proportion of patients who required electrical pacing throughout the study. Likewise, there were no differences between the two study groups in blood pressures or any hemodynamic measurements taken through a Swan-Ganz catheter. The mean durations of stay in the hospital (Celsior, 17 ± 11 days; control, 21 ± 43 days) and intensive care unit (Celsior, 113 ± 78 hours; control, 126 ± 98 hours) were comparable between treatment groups.

**Comment**

The formulation of organ preservation solutions is based on three general principles: (1) reduction of tissue metabolic rate by hypothermia and mechanical arrest, (2) provision of a biochemical medium to maintain tissue viability, and (3) minimization of reperfusion injury [6]. Celsior is an extracellular-type solution designed to fulfill these general principles of organ preservation and to accommodate the specific needs of the myocardium. Celsior addresses these issues by including specific components to prevent cell edema (mannitol and lactobionate), to prevent oxygen-derived free radical injury (reduced glutathione, histidine, and mannitol), to prevent myocyte contracture by enhancing energy production (glutamate), and to limit calcium overload (high magnesium content, slight degree of acidosis).

After the effectiveness of Celsior in heart preservation was demonstrated in preclinical models [10, 11], several small studies suggested the utility of Celsior for preservation of cardiac allografts before clinical transplantation. For example, a recent single-center, randomized study compared Celsior and Custodial (HTK-Brettschneiders) solution in 48 heart transplant recipients (24 patients in
with Celsior impart additional advantages to conventional solutions in high-risk cases must await further evaluations.

In addition to the authors, the following persons participated in this study: Alexandria Berg (Emory University Hospital, Atlanta, GA), Marilyn Ripoll (Alton Ochsner Medical Foundation, New Orleans, LA), Carol Fisher (Temple University Hospital, Philadelphia, PA), Lesley Early (University of Alabama at Birmingham, Birmingham, AL), Diana Zaldonis (University of Pittsburgh, Pittsburgh, PA), Kay Price (University of Kentucky, Lexington, KY), Patty Meldrum (University of Utah, Salt Lake City, UT), Terri Donaldson (Vanderbilt University Medical Center, Nashville, TN), Cyndi Thomas (Texas Heart Institute, Houston, TX), Anne Marie Powell (University Hospital, London, Ontario, Canada), Michele Theunissen (University of Florida, Gainesville, FL), Robert Huizenga (University of Alberta Hospitals, Edmonton, Alberta, Canada), Karol Markowski (University of Toronto, Toronto, Ontario, Canada), Vincent Conti (University of Saskatchewan, Saskatoon, Canada), Sharon Finlay (University of Ottawa Heart Institute, Ottawa, Ontario, Canada), Karin Keller (University of Colorado, Denver, CO), and Jayne Meyer (SangStat Medical Corporation, Fremont, CA).

This study was supported by SangStat Medical Corporation, Fremont, CA.

References

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*Ann Thorac Surg* 2001;71:1442-1447

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