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Original Article

Trillium™-Coated Oxygenators in Adult Open-Heart Surgery: A Prospective Randomized Trial

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Abstract: This randomized, prospective clinical trial examines the impact of the use of Trillium™ biopassive surface coating on clinical outcomes after cardiopulmonary bypass (CPB) that may be induced by contact of blood elements with foreign surfaces. The study consisted of 98 consecutive patients randomly assigned to either a CPB circuit that consisted of a Trillium-coated Affinity open reservoir oxygenator or a CPB circuit with an uncoated Affinity open reservoir oxygenator. The operative procedure performed on all 98 patients consisted of either coronary artery bypass graft (CABG), valve, or a combination of the two. Exclusion criteria consisted of patients who presented to the operating room in circulatory arrest. Trillium biopassive surface coating resulted in improved clinical outcomes and fewer adverse events when compared to the control group. Significantly, fewer patients required no blood products (18.3% in the control group vs. 32.7% in the treatment group), even though the control group had a significantly higher pre-bypass hematocrit. Postoperative atrial fibrillation (24.5% vs. 16.3%) and reoperation for bleeding (10.2% vs. 4.1%) showed a much lower incidence in the Trillium group. Significance was not reached because of the small sample size resulting in low power. Trillium circuits result in improved patient outcomes in the treatment group when compared to the control circuit group. **Keywords:** Trillium, oxygenator, open-heart surgery, outcomes. *JECT. 2002;34:248–253*

The application of extracorporeal circulation and its untoward effects have been well documented (1). The proinflammatory response and complement activation associated with cardiopulmonary bypass (CPB) has been well described (2). Numerous strategies at blunting these untoward effects of CPB have been studied and include heparin-coating techniques (3), the use of leukocyte-depleting filters, (4) and the use of antifibrinolytic agents (5,6).

With regard to heparin-coating techniques, most studies have focused on two different commercially available treatments. The covalently bonded heparin coating, Carmeda (Medtronic Cardiopulmonary, Minneapolis, MN) and the ionically bonded heparin coating, Duraflo II (Baxter Healthcare, Irvine, CA). Both of these biopassive surface coatings have proved to help blunt the complement and proinflammatory responses of CPB (7,8).

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One of the newer coatings is the Trillium™ (Medtronic Cardiopulmonary, Minneapolis, MN) biopassive surface. This coating process involves two polymers. The first functions as a primer that strongly bonds to the surface of most materials used in an extracorporeal circuit. The second polymer is bound to the primer coat and is composed of sulphonate groups, polyethylene oxide chains, and heparin. These groups are covalently incorporated into the coating and are, therefore, nonleaching (9). This study investigates the impact of the use of Trillium biopassive surface coating on clinical outcomes after CPB.

MATERIALS AND METHODS

Study Design

Investigational Review Board committee member reviewed the methodology and granted permission to publish the paper. The study was a randomized, prospective clinical trial. A total of 98 consecutive patients undergoing cardiac surgery with CPB

were randomly assigned to the treatment or control group. The study design was prospective and blind to all caregivers with the exception of the perfusionists. Patients were randomly allocated to either a treatment group or control group.

Cardiac Risk Predictor (Health Data Research, Portland, OR) was used preoperatively to determine predicted mortality and predicted stroke rate, which helped to compare clinical severity and co-morbidities (risk factors) for each patient group. Preoperative data, intraoperative data, and postoperative data were collected prospectively by either a perfusionist and/or data manager nurse. Exclusion criteria consisted of patients who presented to the operating room in circulatory arrest.

Anesthesia and Extracorporeal Circulation

Anesthesia and extracorporeal circulation were standardized. Anesthesia was induced and maintained with a combination of fentanyl (Abbott Laboratories, North Chicago, IL), midazolam (MOVA Pharmaceutical Corporation, Caguas, Puerto Rico), pavulon (Gensia Sicor Pharmaceuticals, Irvine, CA), and complemented with isofluorane (Baxter Healthcare Corporation, Deerfield, IL). Propofol (Gensia Sicor Pharmaceutical Corporation, Irvine, CA) was started en route to the intensive care unit (ICU).

The extracorporeal circuit was standardized using Avecor tubing pack/arterial filter (Medtronic Cardiopulmonary, Minneapolis, MN), oxygenator (Medtronic Cardiopulmonary, Minneapolis, MN) and 4:1 cardioplegia delivery system (Medtronic Cardiopulmonary, Minneapolis, MN). The treatment group consisted of an integrated open reservoir Affinity 541 I-CVR oxygenator (Medtronic Cardiopulmonary, Minneapolis, MN) coated with Trillium™ biopassive surface (TBS). The control circuit was identical but without the biopassive coating. Systemic arterial perfusion was provided with either a roller pump (Sarns/Terumo, Ann Arbor, MI) or a centrifugal pump (Sarns/Terumo Delphin, Ann Arbor, MI). A centrifugal pump was used in cases that had a tendency for prolonged pump times (i.e., combination and redo procedures, see Table 2).

The extracorporeal circuit was primed with Plasma-Lyte-A (Baxter Healthcare-IV Systems, Deerfield, IL), porcine heparin (Elkins-Sinn Inc., Cherry Hill, NJ) 10,000 IU, and sodium bicarbonate (American Pharmaceutical Partner Inc., Los Angles, CA) 25 mEq/L. Porcine heparin (350 IU/kg) was administered before aortic cannulation. Anticoagulation was maintained during CPB by measuring the activated clotting time (ACT) (Medtronic Hemo-Tec, Englewood, CO). An ACT greater than 480 seconds was targeted while on bypass. One quarter of the loading dose of heparin was given at each 60-minute pump time interval. Patients were allowed to "drift" cool to a temperature between 32 and 34°C. Myocardial preservation techniques were comparable among the two study groups. Blood cardioplegia was given antegrade for arrest, with maintenance cardioplegia delivered intermittently retrograde for the duration of the ischemic time period. A cardiotomy suction device was used to return shed mediastinal blood to the systemic circulation. After termination of bypass, heparin neutralization was achieved with protamine (American Pharmaceutical Partner Inc., Los Angels, CA) in a ratio of 0.6 mg for every 100 IU of total heparin administered and confirmed by the return of the ACTs to baseline values. After decannulation, the residual pump blood was returned to the patient without further processing. Following standard protocol, a cell saver (Medtronic Cardiopulmonary, Minneapolis, MN) was used only in cases that were deemed to have a greater propensity to bleed (i.e., recent thrombolytic therapy, reoperations, see Table 2). Amicar or aprotinin was administered based on physician preference. Transfusion thresholds (indications) and protocol were standardized as outlined in the Appendix.

Statistical Analysis

The study data were gathered on customized patient-tracking forms and entered into a database program (FileMaker Pro, Claris Corporation, Santa Clara, CA) where the data were stored and preliminarily analyzed. Further analysis used Minitab, Inc. (State College, PA) and Limdep (Economic Software Inc., Plainview, NY) statistical software. Categorical data were expressed as percentage with *N* (case counts) included, and measured data were expressed as mean ± one standard deviation. Univariate analysis was performed by means of Fisher's exact test on all categorical data and *t*-test on all measured data. A two-sided p of .05 or less was considered to be statistically significant.

RESULTS

No significant differences existed between the two groups in the 29 preoperative risk factors that were analyzed, with two exceptions (see Table 1). The two exceptions were the "last preop HCT" and "hypertension." The "last preop HCT" showed a significantly lower hematocrit in the treatment group versus the control group, and there were significantly more patients with a history of hypertension in the treatment group. The predicted mortality, as calculated by Cardiac Risk Predictor, was similar in the two groups as well as the predicted stroke. Objective and thorough preoperative analysis is extremely important to determine whether the two groups are similar enough to analyze outcome data accurately.

Twenty-five intraoperative management and outcome data elements are listed in Table 2. The operative procedures were not significantly different between the two

Table 1. Preoperative risk factors and variables.

Description	Control n = 49	Treatment n = 49	*p*-Value
Patient age (years)	65 ± 11.5	67 ± 10.7	NS
Antiplatelet therapy within 48 hours before surgery	5 (10.2%)	6 (12.2%)	NS
BSA (M^2)	1.95 ± 0.24	1.95 ± 0.21	NS
Cerebrovascular disease–prior stroke	5 (10.2%)	2 (4.1%)	NS
Cerebrovascular disease–benign disease, no stroke	5 (10.2%)	8 (16.3%)	NS
Congestive heart failure	11 (22.4%)	9 (18.4%)	NS
COPD, treated with steroids	3 (6.1%)	4 (8.2%)	NS
COPD, treated with other than steroids	6 (12.2%)	5 (10.2%)	NS
Diabetes	15 (30.6%)	17 (34.7%)	NS
Drug abuse	1 (2.0%)	2 (4.1%)	NS
Ejection fraction (%)	38 ± 14	43 ± 10	NS
Gender, male	33 (67.3%)	36 (73.5%)	NS
Hypertension	34 (69.4%)	41 (83.7%)	$p < .05$
Last pre-op HCT (%)	36.5 ± 4.4	34.3 ± 4.6	$p < .05$
Left main disease	26 (53.0%)	24 (50.0%)	NS
Myocardial infarction 0–6 Weeks	10 (20.4%)	17 (34.7%)	NS
Myocardial infarction–remote, >6 weeks	9 (18.4%)	11 (22.4%)	NS
Obesity, morbid	6 (12.2%)	3 (6.1%)	NS
Patient refused blood products	0	0	
Pulmonary hypertension–MAP greater than 30 mmHg	0	2 (4.0%)	NS
Peripheral vascular disease	7 (14.3%)	6 (12.2%)	NS
Renal failure–dialysis	0	1 (2.0%)	NS
Renal failure–creatinine 1.5–2.0 mg/dl	0	2 (4.1%)	NS
Renal failure–creatinine >2.0 mg/dl	1 (2.0%)	0	NS
Steroid use	4 (8.2%)	3 (6.1%)	NS
Subacute bacterial endocarditis	0	0	
Predicted mortality (%)	7.0 ± 6.9	5.9 ± 6.5	NS
Predicted stroke (%)	3.8 ± 3.5	3.5 ± 3.0	NS
Predicted transfusion units (red blood cells)	2.3 ± 1.6	2.2 ± 1.3	NS

NS, not significant.

groups; neither was total CPB time, total cross-clamp time, and operating room time. The use of antifibrinolytic agents, aprotinin (Trayslol) (Bayer Corporation Pharmaceutical Division, West Haven, CT) or epsilon aminocaproic acid (Amicar) (American Regent Laboratories Inc., Los Angels, CA) was not significantly different between groups. Only two measures, "use of hemoconcentrator" and "additional volume added during CPB," was significantly different. Significantly more patients in the treatment group required this use of a hemoconcentrator during CPB to remove excess fluid, and coincidentally, the treatment group also required less volume replacement during CPB. The measure of "additional volume added during CPB" was defined as any volume (i.e., drugs, crystalloid, colloid, and blood products) added to the extracorporeal circuit during CPB.

Eighteen postoperative outcome variables were analyzed. Percentage of patients receiving no blood products during their hospital stay was significantly different between groups. This was observed despite the treatment group having a significantly lower preoperative hematocrit. In addition, there were less reoperations for bleeding in the treatment group. There was a trend toward less postop atrial fibrillation in the treatment group. The power of the study was not high enough to observe any significant differences (e.g., to detect significance in the occurrence of atrial fibrillation over 300 patients would be required in each group).

DISCUSSION

One of the main purposes of this unique study was to examine the impact of Trillium™-coated oxygenators on clinical outcomes. Our exclusion criteria (patients presenting to the operating room in circulatory arrest) were minimal, which helped determine whether Trillium™ is beneficial in everyday use and over a broad spectrum of patient demographics and comorbidities. Earlier published studies analyzing Trillium™ either looked at the biochemical response to this coating (10), the effect Trillium™ had on platelets (11), a human trial that analyzed clinical benefits and biochemical results (12), or an animal study focusing on the effects of Trillium™ on clotting and hemolysis (13).

In the present study, we found that both the control and treatment groups were well matched preoperatively, as

Table 2. Intraoperative management and outcomes.

Description	Control n = 49	Treatment n = 49	*p*-Value
CABG	42 (85.7%)	44 (90.0%)	NS
Valve	5 (10.2%)	1 (2.0%)	NS
CABG/valve	2 (4.1%)	4 (8.2%)	NS
First operation	46 (93.9%)	45 (91.8%)	NS
Reoperation, first time	3 (6.1%)	3 (6.1%)	NS
Reoperation, second time	0	1 (2.0%)	NS
Elective	44 (89.8%)	42 (85.7%)	NS
Urgent	3 (6.1%)	6 (12.2%)	NS
Emergent	2 (4.1%)	1 (2%)	NS
Trayslol, full dose	24 (50.0%)	24 (50.0%)	NS
Trayslol, half dose	1 (2.0%)	0	NS
Amicar	24 (50.0%)	25 (51.0%)	NS
Hemoconcentrator	9 (20.4%)	20 (40.8%)	$p < .05$
Cell saver	10 (20.4%)	6 (12.2%)	NS
IABP insertion, pre-op	4 (8.2%)	7 (14.3%)	NS
IABP insertion, intra-op	2 (4.1%)	2 (4.1%)	NS
Roller	43 (87.7%)	42 (85.7%)	NS
Centrifugal	6 (12.2%)	7 (14.3%)	NS
Lowest HCT on CPB (%)	22.4 ± 2.9	21.5 ± 3.2	NS
Spontaneous rhythm achieved after removal of cross clamp	31 (63.2%)	37 (75.5%)	NS
Additional volume added during CPB (cc)	904 ± 900	632 ± 670	$p < .05$
Urine output on CPB (cc)	459 ± 388	353 ± 214	NS
Total pump time (minutes)	107 ± 32	110 ± 32	NS
Total cross clamp time (minutes)	89 ± 25	92 ± 25	NS
Total O.R. room time (minutes)	337 ± 97	330 ± 77	NS

NS, not significant.

evidenced by the lack of significant differences in the measures presented in Table 1. There were no adverse effects related to the use of the Trillium™-coated oxygenator. The use of the Trillium™-coated oxygenator was strongly associated with decreased frequency of administration of any blood products (red blood cells, fresh frozen plasma, and platelets). We also found a trend in favor of the Trillium™-coated oxygenator when we looked at the need to return to the operating room for treatment of post-op thoracic bleeding. Furthermore, the Trillium™ group required more frequent use of a hemoconcentrator to remove excess volume and also required less volume replacement while on CPB. Perhaps the improved fluid requirements in the treatment group can be explained by the reduction of complement activation afforded by the Trillium™ coating causing less capillary leakage. Similar outcomes have been described elsewhere when using heparin-coated circuits and full heparinization (14).

Last, we observed a trend toward a lower incidence of postop atrial fibrillation in the treatment group. Similar observations with different heparin surface coatings have been reported elsewhere (15,16). The reason for this decrease in morbidity is not known, because the cause of postop atrial fibrillation in cardiac surgery patients is not well understood (17). Some hypothesize that the reduced incidence of atrial fibrillation in patients exposed to biocompatible extracorporeal circuits could be related to the beneficial effects of coated surfaces on the inflammatory response (18). Postoperative atrial fibrillation is common after coronary artery bypass graft (CABG) surgery with an incidence rate between 17–30%. Although both treatment and control groups were within this range, the treatment group had a 33% lower occurrence of postoperative atrial fibrillation.

The occurrence of postoperative atrial fibrillation has a significant impact on both intensive care units and overall hospital stay, which, in turn, dramatically affects costs. Furthermore, a recent study (19) showed that a reduction in the incidence of postoperative atrial fibrillation might improve neurocognitive function. Factors influencing the risk of postoperative atrial fibrillation include demographic factors (i.e., male sex), and certain surgical practices (i.e., pulmonary vein venting, bicaval cannulation) (17). Randomized controlled trials are necessary to determine if modification of these surgical practices and/or the extracorporeal circuit would decrease the incidence of postoperative atrial fibrillation.

The process of extracorporeal circulation and its associated coagulopathy and morbidity is a huge challenge to overcome in cardiac operations. We think Trillium™-coated circuits, (even with full dose heparinization and cardiotomy suction), can help curtail the delicate hemostatic balance. Perhaps further strategies focusing on reducing blood activation may prove even more beneficial. These strategies could include lower heparin doses, the use of a closed venous reservoir, elimination of car-

Table 3. Postoperative outcome data.

Description	Control n = 49	Treatment n = 49	*p*-Value
ICU length of stay (days)	2.9 ± 2.6	2.7 ± 4.0	NS
Post-op length of stay (days)	6.4 ± 3.7	6.1 ± 3.8	NS
Ventilator time (hours)	28.3 ± 54.9	38.9 ± 97.2	NS
Post-op atrial fibrillation	12 (24.4%)	8 (16.3%)	NS
Pulmonary edema	4 (8.2%)	6 (12.2%)	NS
Pneumonia	1 (2.0%)	0%	NS
ARDS	2 (4.1%)	5 (10.2%)	NS
No blood products administered	9 (18.3%)	16 (32.7%)	$p < .05$
Total blood products (units) (rbc + ffp + plt)	8.35 ± 10.1	7.12 ± 9.9	NS
RBC (units)	2.4 ± 2.2	2.3 ± 2.8	NS
FFP (units)	0.9 ± 2.0	0.8 ± 1.7	NS
Platelets (units)	5.0 ± 7.0	3.9 ± 6.4	NS
Observed mortality (%)	2 (4.1%)	1 (2.0%)	NS
Pt returned to OR for tx of post-op thoracic bleeding	5 (10.2%)	2 (4.1%)	NS
Post-op sternal infection	2 (4.1%)	1 (2.0%)	NS
Pt had a CVA intra or postoperatively	3 (6.1%)	3 (6.1%)	NS
Post-op leg wound infection	0	0	NS
Post-op cardiac arrest	0%	1 (2.0%)	NS

diotomy suction, aprotinin administration, leukocyte depleting filters, and so forth.

Two large, prospective randomized studies (20) were performed and showed that the use of heparin-bonded circuits with lower anticoagulation resulted in markedly improved clinical outcomes in patients undergoing primary CABG surgery with a reduction in both clinical and microscopic thromboembolic risks. This study (20) protocol also included closed venous reservoirs, elimination of cardiotomy suction, and all blood from the operative field was directed to the cell saver.

The results presented here suggest the need for further research on the use of this biopassive coating. A larger randomized, controlled trial would provide the most compelling evidence for the impact of this biopassive coating on patient outcomes following CPB. Careful consideration of evidence regarding patient outcomes should be a major factor in the decision of circuit components and circuit type used.

An earlier prospective, randomized trial showed no clinical benefits or clinically important biochemical results when analyzing Trillium™-coating (12). A plausible explanation for these differing results might be attributable to the small sample size ($N = 30$), low-risk category of patient selection, and short CPB times ($\leq$77 minute average). Wahba and colleagues (21) demonstrated that the duration of CPB affects thrombin formation as well as platelet count and function that leads to an increased need for transfusions of red blood cells.

Our study provides evidence of a trend in improved clinical outcomes for patients with the use of Trillium™ biopassive surface. Significantly fewer patients in the treatment group required the use of any blood products. Trends in decreased probability of developing atrial fibrillation postoperatively and a decreased incidence in reoperation for bleeding were observed.

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APPENDIX

Indications to Transfuse Perioperative Blood/ Components

$$\text{*Allowable Blood Loss} = \frac{(\text{HCT original} - \text{HCT allowed}) \times \text{estimated blood volume}}{\text{HCT average}}$$

Red Blood Cells

- Exceeds allowable blood loss
- Chronic anemia, Hgb <8gm/dl and pulse >100
- Hgb <10gm/dl and pre-existing disease necessitating higher Hgb
- Hgb <10gm/dl and on-going blood loss
- HCT <20% on CPB
- Used for CPB pump prime to avoid excessive hemodilution

Platelets

- Platelet count <50,000 $\times 10^3$ cu mm
- Cardiovascular surgery platelet count <100,000 $\times 10^3$ cu mm after reversal of heparin and bleeding/oozing documented
- Antiplatelet drugs given in last 24 hours or aspirin in last 5 days
- Clinical oozing/bleeding after protamine reversal with normal ACT.

Fresh Frozen Plasma

- Reversal of Warfarin in urgent circumstances, and presence of oozing/bleeding with a PTT >50 seconds, PT >20 seconds
- PTT >50 seconds or PT >20 seconds
- Liver disease
- Treatment of clotting factor deficiencies
- Clinical oozing after protamine reversal not related to surgical causes

Cryoprecipitate

- Fibrinogen concentration < 100mg/dl
- Active bleeding – used as "Fibrin Glue"
- Prolonged bleeding time >9minutes