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Evaluation of Biocompatible Cardiopulmonary Bypass Circuit Use During Pediatric Open Heart Surgery

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Abstract: The contact of blood with nonbiological surfaces during cardiopulmonary bypass (CPB) induces a whole body inflammatory response and increases postoperative morbidity directly related to bleeding complications and end organ dysfunction. Methods to reduce these effects have included modification of extracorporeal circuits through biocompatible coating of disposables and the application of various pharmacological agents. Biocompatible coated surfaces are designed to mimic physiologic surfaces. This study was designed to ascertain the effects of using coated circuits during pediatric CPB. After Institutional Review Board approval and parent/guardian consent, patients undergoing CPB, weighing less than 15 kg, with target CPB temperatures more than 28°C, were enrolled into the Coated Circuit Group using an entirely biocompatible CPB circuit with poly(2-methoxyethylacrylate) (PMEA) and a biocompatible coated oxygenator ($n = 16$). Those patients were retrospectively matched to control patients having the same congenital repair with respect to patient size, surgeon, anesthesiologist, bypass time, cross-clamp time, bypass temperature, and noncoated bypass disposables; ($n = 16$). CPB data collected included on-bypass platelet count, hematocrit (HCT), and CPB blood product use. Postprotamine data collected in the operating room included blood product use, time from initial protamine administration to chest closure, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). Postoperative intensive care unit (ICU) data included blood product use, HCT, chest tube output, platelet count, PT, aPTT, INR, blood gases, lactate, and ventilator settings at 1, 2, 4, 6, 12, and 24 hours. Other data collected included intubation time, length of time to chest tube removal, and length of ICU stay. Statistical significance ($p < .05$) was seen in units of platelets transfused postprotamine, ventilator peak inflation pressure (PIP) on admission to the ICU, postoperative day 0 packed red blood cells (PRBC) and fresh frozen plasma (FFP) transfused, and lactate at 1, 2, 4, 6, and 12 hours postoperative. Several parameters approached statistical significance, including PRBC transfused postprotamine, time from protamine administration to chest closure, postoperative day 0 platelets transfused, and ICU stay. The data suggest that PMEA biocompatible CPB circuits can be used safely during pediatric heart surgery, resulting in a decrease in postoperative blood product use, improved postoperative lung function, and a reduction in the time spent in the ICU. **Keywords:** immune response, pediatric cardiopulmonary bypass, biocompatible circuits, 2-methoxyethylacrylate, congenital heart surgery. *JECT. 2006; 38:22–26*

The continuous interaction of blood with artificial contact surfaces during cardiopulmonary bypass (CPB) can lead to substantial damage of blood cells and plasma factors (1). Contact activation leads to bleeding complications, organ dysfunction, and many other adverse physiological effects. The greatest potential for activation of complement or hematologic damage during CPB is from blood exposure to nonbiological surfaces. The fusion of turbulent flow patterns, zones of blood stasis, and aspiration of shed blood contribute to contact activation and damage to the formed elements of blood.

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The process of extracorporeal circulation results in dramatic changes to both biochemical and cellular elements of blood, disrupting the hemostatic balance. When blood contacts foreign materials of the extracorporeal circuit (ECC), platelets adhere to the surface, and factor XII is activated, initiating clotting (2). Clotting factor activation occurs, and subsequent activation of kallikrein, the kinin-bradykinin system, and the fibrinolytic and complement cascades are initiated. The activation of complement has been shown to release anaphylatoxins, which further cascade the inflammatory reaction (3,4). The hemostatic abnormalities resulting from cardiac surgery with CPB result from a number of factors that include both qualitative and quantitative platelet dysfunction, hyperfibrinolytic activity, coagulation deficits, and loss of vascular integrity (5–8). This blood–surface interaction induces a whole body inflammatory response and increases postoperative mor-

bidity, which encompasses bleeding complications and multiorgan dysfunction. The blood–surface interaction has been shown to cause capillary leak syndrome, microvascular lung injury, and increased blood product use (9,10).

Methods to reduce the effects of CPB have included modification of extracorporeal circuits through biocompatible coating of the disposable devices, modified ultrafiltration, return of shed blood from the pericardium to the cell saver, normothermic CPB, and the application of various pharmacological agents (11). Most coated materials are designed to mimic physiologic surfaces (12). This study was designed to ascertain the effects of CPB when using coated circuits with poly(2-methoxyethylacrylate) (PEMA; also known as Terumo X Coating; Terumo Medical Corporation, Ann Arbor, MI) by measuring operative and postoperative bleeding and the ability to suppress the inflammatory response to extracorporeal circulation in a pediatric model by indirectly evaluating the response through patient gas exchange, need for ventilatory support and settings, and total stay in the intensive care unit (ICU).

METHODS

After Institutional Review Board approval and parent/guardian consent, patients undergoing CPB, weighing less than 15 kg, with target CPB temperatures more than 28°C, were enrolled into the coated circuit group (CC), using a biocompatible coated CPB circuit with the exception of the cannula and hemofilter. The coated disposables consisted of Terumo X Coated tubing (3/16 in and ¼ × 3/32-in polyvinyl chloride (PVC) tubing for the arterial-venous (AV) loop), a Terumo Baby RX Oxygenator with X Coating or a Cobe (Cobe Cardiovascular, Arvada, CO) Physio Coated (phosphorylcholine coated biocompatible coating) Lilliput I or II oxygenator (open system), roller pump, Terumo HCO5 hemofilter (not coated), Cobe 4:1 Vanguard pediatric blood cardioplegia device (coated with the exception of the heat exchanger), and a coated Terumo AFO2 arterial line filter (ALF) with X Coating ($n = 16$; April 2004 to November 2004). Those patients were retrospectively matched to control patients having the same congenital repair with respect to patient size, surgeon, anesthesiologist, bypass time, cross-clamp time, bypass temperature, and noncoated bypass disposables (NC, $n = 16$; July 2003 to March 2004). The disposables for the noncoated group included a Terumo Baby RX or Cobe Lilliput I or II oxygenator (open system), roller pump, Terumo HCO5 hemofilter, Terumo AFO2 arterial line filter, Cobe 4:1 Vanguard pediatric blood cardioplegia device, and standard 3/16 in and ¼ × 3/32-in PVC tubing for the AV loop. The prime consisted of PlasmaLyte-A crystalloid, 1 unit packed red blood cells, 100 mL of 25% albumin, heparin at 2 U/mL of prime solution, and 15 mEq sodium bicarbonate. CPB data collected included on-bypass platelet count, hematocrit (HCT), and on-bypass blood product use. Postprotamine reversal of heparin data collected in the operating room included blood product use, time from initial protamine administration to chest closure, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and last operating room (OR) ventilator settings. All OR procedures were accomplished with the same ventilator using pressure controlled ventilation. Postoperative ICU data included blood product use, HCT, chest tube output, platelet count, PT, aPTT, INR, blood gases, including lactate levels, and ventilator settings at 1, 2, 4, 6, 12, and 24 hours. Other data collected included intubation time, length of time until chest tube removal, and length of ICU stay.

RESULTS

Tables 1 and 2 describes the demographic data, with no statistical difference seen between the two groups. The data collected in the OR showed significantly less platelets transfused postprotamine reversal of heparin in the CC patients (CC = 0.4 ± 0.5 units and NC = 0.7 ± 0.5 units, $p = .04$; Figure 1). The time from protamine reversal of heparin to chest closure also approached significance favoring the CC group (CC = 28 ± 8.5 minutes and NC = 35 ± 8.5 minutes; $p = 0.1$). No other statistical significance was seen in the last OR PT, aPTT, INR, platelet count, or HCT. Significance was seen in last OR ventilator peak inflation pressure (PIP) settings, with higher settings seen in the NC group (CC = 22.3 ± 1.4 cm H_2O and NC = 23.5 ± 1.4 cm H_2O; $p = .04$; Figure 2). Statistical significance

Table 1. Patient demographic.

	CC	NC
Height (cm)	73 ± 20	69 ± 20
Weight (kg)	8.5 ± 5	7.6 ± 5
Preoperative Plts (K)	331 ± 67	299 ± 67
Preoperative HCT (%)	35 ± 5	37 ± 5
Prime vol (mL)	600 ± 100	550 ± 100
Prime HCT (%)	29 ± 3	29 ± 3
CPB Tm (min)	73 ± 40	85 ± 40
XC Tm (min)	39 ± 19	44 ± 19
Temperature (°C)	32 ± 2.5	31 ± 2.5
On CPB Plts (K)	89 ± 24	82 ± 24

Table 2. Surgical procedures performed per study group.

CC	Repair	NC
3	AVSD	3
9	VSD	9
1	ASD	1
1	Hemi-Fontan	1
1	TOF	1
1	Fontan	1

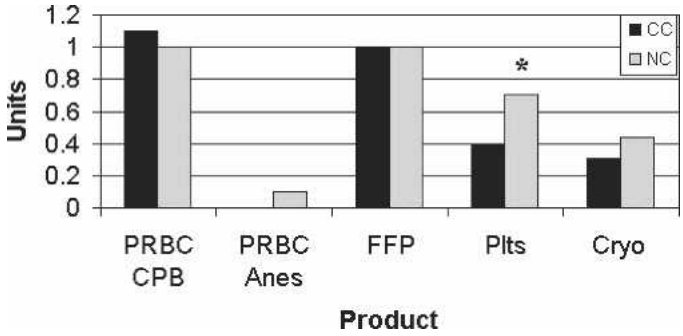

Figure 1. Average operative blood product use (*$p < .05$).

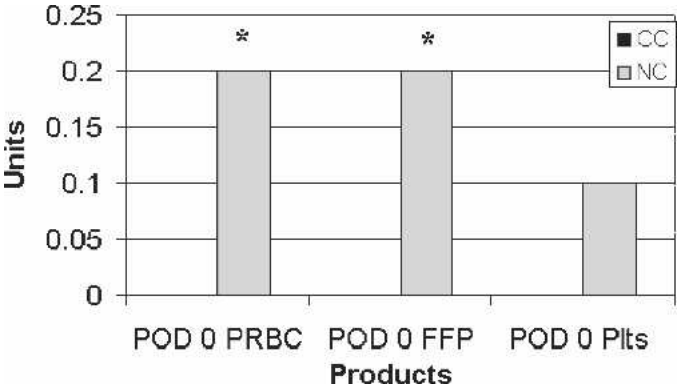

Figure 3. Twenty-four-hour postoperative blood product use (*$p < .05$).

was also seen in 6-hour ICU ventilator mean airway pressure (MAP), with lower pressure seen in the CC group (CC = 8.4 ± 1.2 H_2O and 9.6 ± 1.2 H_2O; $p = .03$). No statistical significance was seen with chest tube loss postoperatively or other ventilator settings. Statistical significance was seen in postoperative day 0 packed red blood cells (PRBC) and fresh frozen plasma (FFP) transfusion, favoring the CC group (PRBC: CC = 0 units and NC = 0.2 units, $p = .04$; FFP: CC = 0 units and NC = 0.2 units, $p = .04$; Figure 3). Statistical significance was also seen in lactate levels at 1 (CC = 1.1 ± 0.2 mM and NC = 1.5 ± 0.2 mM; $p = .04$), 2 (CC = 1.0 ± 0.3 mM and NC = 1.7 ± 0.3 mM; $p = .002$), 4 (CC = 1.2 ± 0.5 mM and NC = 2.2 ± 0.5 mM; $p = .014$), 6 (CC = 1.2 ± 0.3 mM and NC = 1.8 ± 0.3 mM; $p = .048$), and 12 hours postoperatively (CC = 0.9 ± 0.4 mM and NC = 1.3 ± 0.4 mM; $p = .03$; Figure 4). No statistical significance was seen in chest tube time or time on ventilatory support. Total ICU time approached significance because the patients in the CC group spent less time in the ICU (CC = 42 ± 31 hours and NC = 57 ± 31 hours; $p = 0.1$; Figure 5).

DISCUSSION

Much research has been done showing the biocompatible effects of heparin-coated CPB circuits, especially in the preservation of hemostasis and pulmonary function after CPB because of a suppression of the inflammatory response to extracorporeal circulation (13–15). PMEA is a second-generation amphiphilic organic polymer biocoating consisting of a hydrophobic backbone with pendant hydrophilic groups. PMEA has been reported to reduce protein and platelet adsorption and platelet aggregation in in vitro and ex vivo studies (16). Because the outer side of the PMEA molecule is inactive chemically, once PMEA is bound to the circuit tubing, the surface has little tendency to react with blood components. Recent research shows that PMEA decreases the adsorption of blood platelets and several plasma proteins related to the coagulation and fibrinolytic systems in adult models (17). PMEA-coated CPB surfaces have also been shown to improve thrombogenicity, reduce bradykinin release, cause less platelet activation, and reduce the release of proinflammatory cytokines compared with noncoated groups (18). PMEA has been shown to be superior to heparin coating in platelet preservation and is equivalent to heparin coating in terms of the perioperative clinical course and inhibition of inflammatory cytokines (although slightly inferior in the reduction of complement activation) (19,20). PMEA circuits have also been shown to suppress perioperative complement and leukocyte activation when compared with noncoated circuits (17).

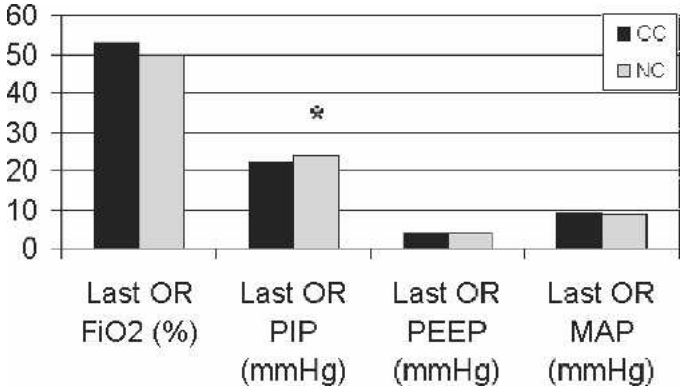

Figure 2. Last OR average mechanical ventilator settings (*$p < .05$).

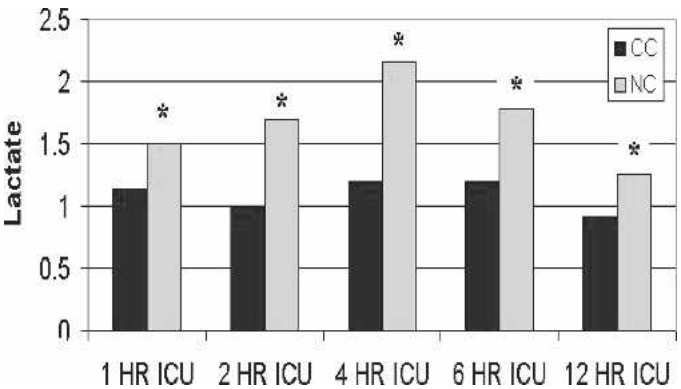

Figure 4. Twenty-four-hour postoperative lactate levels (*$p < .05$).

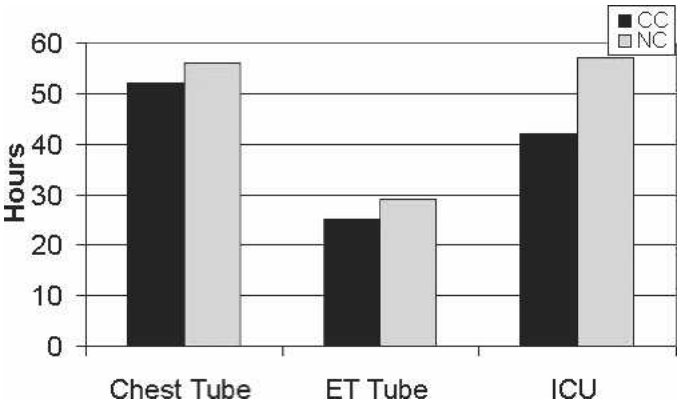

Figure 5. Postoperative times.

The data from this study corroborates much of the data previously collected on PMEA in adult models. The amount of platelets transfused postprotamine was significantly less than that for the NC group. Although the amount transfused was small (0.4 vs. 0.7 units), this represents a reduction in the number of patients receiving an additional random unit blood donor exposure. Although not statistically significant, the amount of PRBCs transfused in the OR approached significance (CC = 0 units, NC = 0.1 units), again reducing the potential for an additional random unit blood donor exposure. This was also seen in postoperative day 0 blood transfusion requirements. The time from protamine reversal of heparin to chest closure also approached statistical significance (CC = 28 ± 8.5 minutes and NC = 35 ± 8.5 minutes; $p = 0.1$), showing a reduced amount of time to chest closure in the CC group, suggesting less postprotamine bleeding. This time may also represent a reduction in OR time as well.

As reported previously with the use of coated circuits, our data also suggested better post-CPB lung function, with significance seen in last OR ventilator PIP settings and also in 6-hour ICU ventilator MAP, favoring the coated circuit group. This data may suggest an attenuation of the immune response to CPB, thus preserving lung function after CPB and postoperatively. Although not statistically significant, total mechanical ventilator time was reduced in the CC group as well (CC = 25 hours and NC = 29 hours), also suggesting improved pulmonary recovery time. Although these data are statistically significant, there is probably little clinical significance. The addition of more patients to this study might have further supported and strengthened this finding.

Because the immune and complement cascades are activated, capillary leakage may occur, causing lactate to be washed out from the underperfused distal vascular beds. The lower lactate levels seen in the CC group at 1, 2, 4, 6, and 12 hours postoperatively suggest a possible reduction in the immune response. The transfusion of stored blood components to the NC group may also explain the elevated levels, because those products can be an additional source of lactate. This may also be related to improved pulmonary function.

The total ICU time approached significance, with the CC group spending approximately 15 hours less, translating into 1 day in the ICU less than the NC group (CC = 42 hours vs. NC = 57 hours). This may be reflective of the reduced ventilatory time, reduced chest tube time, and reduction in lactate levels and transfusion.

The fact that this study was not prospective, blinded, and randomized was a weakness of the design. However, blinding to the perfusionist would have been difficult and almost impossible because of the obvious external characteristics of coated tubing and components. The sample size of the studied population may also be a limitation, although the purpose of the study was to validate a change in our practice, ensuring there would be no harm to the patient as a result of the change, which we did accomplish through the study. The size was also large enough to observe trends from the norm or controls.

CONCLUSION

The data from this study suggest that PMEA biocompatible CPB circuits can be used safely during heart surgery, resulting in a decrease in postoperative blood product use, improved postoperative lung function, and a reduction in the time spent in the ICU in a pediatric model. A prospective, randomized trial looking specifically at immune complexes and complement activation should be undertaken to substantiate these findings. Additionally, there have been no complications or contraindications reported from the use of PMEA circuits.

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