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Clinical Evaluation of Poly(2-methoxyethylacrylate) in Primary Coronary Artery Bypass Grafting

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Abstract: In an attempt to make cardiopulmonary bypass (CPB) less traumatic for patients undergoing cardiac surgery, extracorporeal circuits (ECC) have been modified to achieve this goal. Poly(2-methoxyethylacrylate) (PMEA, X-coating™) is a new polymer coating used in the ECC. PMEA studies have shown excellent biocompatibility with the components of blood. In this evaluation, PMEA-coated ECC were compared with control (CTR) circuits with emphasis on hematological parameters, perioperative homologous blood product usage, and clinical outcomes. Patients undergoing elective coronary artery bypass grafting were randomized to either a PMEA group ($n = 30$) or a CTR group ($n = 30$). Extracorporeal circuit components in the PMEA group were coated except for the cardioplegia delivery device and cannulas. Patients in the CTR group had just the arterial line filter coated. The following hematological parameters were measured: platelet count (PLT), white blood cell count (WBC), red blood cell count (RBC), and hematocrit (Hct). Blood product usage was observed along with clinical outcomes for the following parameters: ventilation time, mediastinal tube output, intensive care unit (ICU) and hospital lengths of stay. The preoperative patient profiles were comparable between the two groups. The PMEA group had marginally higher CPB times (134 ± 31.9 vs. 118 ± 33.7 minutes) and cross clamp times (83.9 ± 21.3 vs. 73.7 ± 21.6 minutes), however no significant differences were reached. Platelet count, RBC, and Hct levels were also comparable between groups with no significant differences. However, there was a significant difference in WBC between groups ($p = 0.041$). Less platelets were administered both intraoperatively and 48 hours postoperatively in the PMEA group. The authors evaluated PMEA-coating by measuring clinical outcomes, such as ventilation time, ICU and hospital lengths of stay, and homologous blood utilization. PMEA patients trended towards less homologous blood transfusions, which helped save an average of $83.41 per patient. Further clinical studies are needed to evaluate the benefits of this new polymer coating. **Keywords:** poly(2-methoxyethylacrylate) (PMEA, X-coating™), biocompatibility, surface modification, cardiopulmonary bypass. *JECT. 2005;37:23–31*

The introduction of cardiopulmonary bypass (CPB) has shaped surgical strategies for the correction of pediatric congenital anomalies as well as adult acquired cardiac disease. However, use of the extracorporeal circuit (ECC) is not without disadvantages. When blood is exposed to artificial surfaces of the ECC, plasma proteins become adsorbed to the synthetic surfaces (1,2). A systemic inflammatory response ensues with complement and leukocyte activation, and release of endotoxin and inflammatory mediators, which contributes to tissue injury (3,4). Systemic inflammatory response caused by bioincompatibility of the ECC is a major concern.

In an effort to decrease the activation of biological systems as a consequence of the ECC, methods of attaching bioactive molecules to nonendothelialized surfaces of the ECC have been researched and introduced into clinical practice. Surface modification using heparin bonded to the surface of polymers in the ECC was one of the earliest interventional approaches to moderating surface contact activation. Heparin can be attached to materials according to various techniques: those that release heparin and those to which heparin is irreversibly bound (5). When used clinically, there is evidence that inflammation related to complement activation is decreased and this may be responsible for improved clinical outcomes after CPB (6,7).

Besides heparin coating, other studies have investigated various types of surface modifications. First, the attachment of nitric oxide on the surface of the ECC has been shown to reduce platelet consumption and eliminate the need for systemic heparinization in an animal model (8). Second, silicone-coated oxygenators have been shown to suppress the release of proinflammatory marker, and were associated with better clinical outcomes (9). Third, surface-modifying additives revealed significantly less plate-

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let deposition on the ECC, whereas complement activation measured by C3a were similar between experimental and control (CTR) groups (10). In addition, phosphorylcholine coating has been investigated clinically by De Somer et al., and appeared to have favorable effects on platelets (11).

Recently, Terumo Corporation (Tokyo, Japan) has developed a surface modification for the ECC, which is engineered to influence protein adsorption and platelet adhesion. Poly(2-methoxyethylacrylate) (PMEA, X-coating™) is composed of an amphiphilic polymer, which is attributed to its hydrophobic and hydrophilic properties. Although PMEA is hydrophobic where it contacts the ECC surface, its blood contact surface is hydrophilic. The surface would have little tendency to react with blood components due to the outer side of the molecule being inactive chemically. There are promising data from in vitro and in vivo animal models supporting the potential improved biocompatibility of PMEA (12,13). The purpose of this investigation was to clinically evaluate PMEA-coated ECC in terms of hematological parameters, homologous blood transfusions, and clinical outcomes.

MATERIALS AND METHODS

Experimental Protocol

From July 2002 to November 2003, patients undergoing elective primary coronary artery bypass grafting (CABG) were randomly allocated to either a PMEA ($n = 30$) or CTR group ($n = 30$). All components of the ECC in the PMEA group were coated except for the cardioplegia delivery device and cannulas. Extracorporeal circuit components in the CTR group were noncoated except for the arterial line filter. Surgeons and anesthesiologists were blinded from this randomization throughout the study. Individuals with preoperative coagulopathy or impaired organ function other than myocardial ischemia were excluded from the study. Other exclusion criteria included the following: weight less than 60 kg; ejection fraction less than 30%; patients on intra-aortic balloon pump; cerebral vascular accident, history of transient ischemic attack or stroke; peripheral vascular disease; bleeding disorders; anemia; thrombocytopenia; antiplatelet therapy (unless stopped 10 days prior to surgery); fibrinolytic therapy (unless stopped 48 hours before surgery); respiratory dysfunction, including chronic obstructive disease, emphysema, severe asthma, bronchitis; renal and hepatic disease; and any type of cancer.

All adult patients undergoing elective CABG were expected to be on CPB for a duration of 60 minutes to be eligible for the evaluation. Surgical technique and anesthesia were the same for both groups. No changes were made in the patients' clinical management; however, there were additional laboratory tests during CPB. The director of hospital laboratory services was contacted about the evaluation and any additional laboratory charges were not forwarded to patients.

An integrated blood conservation strategy was applied uniformly to all patients undergoing the evaluation. The strategy included maximal cell saving, minimizing hemodilution, routine use of an antifibrinolytic, hemoconcentrator, and a concerted effort by the surgeons, anesthesiologists, and perfusionists to minimize homologous blood transfusion. Surgeons evaluated hemostasis based on activated clotting time (ACT), platelet count (PLT), routine coagulation tests, bleeding intraoperatively, and mediastinal tube output before prescribing an order for platelets or any other blood products. The hematocrit (Hct) was maintained greater than 20% on CPB and post-CPB. Platelet count was maintained greater than 100×10^3 mcL^{-1} post-CPB. Fresh frozen plasma and/or cryoprecipitate were ordered if the prothrombin time (normal values: 10–12.4 seconds), partial thromboplastin time (normal values: 23–34 seconds), and INR (normal values: 2–3.5) were prolonged and after the surgeons evaluated the patient's bleeding intraoperatively and mediastinal tube output postoperatively. These transfusion thresholds were adhered to in the 48 hours postoperative period in both groups.

After premedication with versed, patients were induced with etomidate, fentanyl, vecuronium, and anesthetic maintenance was established with propofol and/or inhalation agents. Antibiotics were administered intravenously for infection prophylaxis. Vasoactive agents were titrated accordingly to patient condition and surgical demands. Epsilon-aminocaproic acid (Amicar) was given three times: after induction, in the pump prime, and post-CPB. After endotracheal intubation, patients received ventilation to normocapnia with an oxygen and air mixture. Radial artery and thermodilution pulmonary artery catheters were placed for hemodynamic measurements and procurement of blood samples.

CPB

All disposable ECC components used for this evaluation were products of Terumo Cardiovascular Systems (Ann Arbor, MI). Nonpulsatile CPB was performed using a membrane oxygenator (Capiox SX18), centrifugal pump (SP45), and a 38-μm arterial filter. Total priming volume of the ECC consisted of 1500 mL of Plasmalyte A, 10,000 IU of heparin, 25 g of albumin, 25 g of mannitol, 2 g of magnesium sulfate, and 5 g of Amicar (Wyeth-Ayerst, Madison, NJ). A standard cannulation technique was used with cannulas placed in the ascending aorta and right atrium. After systemic heparinization (300 IU kg^{-1}) was accomplished, CPB was initiated when the ACT was greater than 400 seconds. The left ventricle was vented via the aortic root. Blood from the pericardial cavity was collected to the autotransfusion device, processed, and re-

turned to the patient. The patient's venous saturation and Hct were continuously monitored in-line during CPB utilizing the Sarns CDI 100 (Terumo Cardiovascular Systems). A hemoconcentrator (HC11) was used to increase the Hct level while attempting to reduce blood utilization where large blood volume and/or large amounts of irrigation were returned to the perfusion circuit. Flow rates were maintained between 1.8 to 3.0 L min^{-1} m^{-2}. Patients were allowed to drift to 32°C bladder temperature. After the aorta was cross-clamped, all patients received 750 mL to 1 L, 2°C of 4:1 blood to crystalloid high potassium cardioplegia solution for myocardial protection. Distal anastomoses of the grafts were placed during aortic cross clamping, and proximal anastomoses were constructed with a side-biter clamp after 3 minutes of normothermic, all blood, hot shot, and aortic cross-clamp release. Acid-base balance was managed according to the alpha-stat concept. Patients were weaned from CPB with the use of inotropic support if necessary. After termination of CPB, heparin was neutralized by an equal dose of protamine sulfate at 1 mg per 100 IU of total heparin administered. Blood from the ECC was aspirated to the autotransfusion device, processed, and washed before returning to the patient.

Blood Sample Collection

Blood samples were drawn for hematological assessment, which included PLT, white blood cell count (WBC), red blood cell count (RBC), and Hct. All baseline values for hematology were collected before the day of the patient's scheduled surgery. Platelet count was examined at baseline, 30 minutes on CPB, prior to termination of CPB, and 10 minutes post-protamine. White blood cell and RBC counts were measured at baseline, 60 minutes on CPB, and 30 minutes after patients were transported to the intensive care unit (ICU). Hematocrit was also examined at baseline, 60 minutes on CPB, and 10 minutes post-protamine. Samples collected prior to termination of CPB were collected during proximal anastomoses and will be referred to as P-pump.

Clinical Outcomes

All patients were followed after the procedure until discharged. Blood product usage was recorded for the intraoperative procedure and 48 hours postoperatively. Mediastinal tube output also was documented for 48 hours postoperatively. Ventilation time, ICU and hospital lengths of stay were tracked and recorded. Finally, cost data for various departments were recorded and analyzed between groups. The departments consisted of anesthesia, surgery, respiratory therapy, ICU, and stepdown unit.

Statistical Analysis

All data were recorded and entered into a computer database. Patient characteristics and perioperative data were collected and compared between the two groups with *t* tests and chi-square tests for continuous and categorical variables respectively. When categorical variable cell counts were small, Fisher's exact test was used to evaluate significance. Repeated-measures analysis of variance models were used to examine coating effects on PLT, WBC, RBC, and Hct over time. This model allowed the measurements for each patient to be correlated. The outcome of interest for PLT, WBC, RBC, and Hct were the measured levels. Each of the models included fixed coating and time effects, along with a fixed coating and time interaction. A significant interaction would imply that the coating effect differs with time. For significant effects, pairwise comparisons were made and *p* values were adjusted for multiple comparisons with Tukey's method. *p* values were considered to be significant if less than 0.05. SAS software (SAS Institute Inc., Cary, NC) was used for the analyses. Data are presented as mean ± standard deviation or N (%).

RESULTS

The preoperative patient profiles were comparable between the groups (Table 1). No significant differences existed between the groups in terms of age, body surface area, ejection fraction, and risk factors. The groups were well matched with respect to operative surgical staff. There was no statistical significance between the two surgeons, anesthesiologists, and perfusionists between groups. Twenty-nine patients in the PMEA group had their left internal mammary artery (LIMA) used along with saphenous vein, and one patient had all saphenous vein grafts. In the CTR group, 28 patients had LIMA grafts along with saphenous vein, and two patients had all saphenous vein grafts. The PMEA group tended to have fewer females, but the difference did not reach statistical significance.

Table 1. Preoperative patient profiles of the CTR and PMEA groups.

	CTR (n = 30)	PMEA (n = 30)	p Value
Age	62.4 ± 11.2	64.3 ± 7.6	NS
Gender			
Female	10 (33%)	3 (10%)	NS
Male	20 (67%)	27 (90%)	
Body surface area (m^2)	2.06 ± 0.2	2.03 ± 0.2	NS
Ejection fraction (%)	58.1 ± 14.1	61.9 ± 13.3	NS
Risk factors			
Diabetes mellitus	4 (13%)	9 (30%)	NS
Hypercholesterolemia	4 (13%)	4 (13%)	NS
Hyperlipidemia	4 (13%)	6 (20%)	NS
Hypertension	17 (57%)	21 (70%)	NS
Left main disease	2 (7%)	2 (7%)	NS
Previous myocardial infarction	8 (27%)	11 (37%)	NS
Obesity	2 (7%)	2 (7%)	NS

Table 2 depicts the perioperative patient data compared between the two groups. The PMEA group had marginally higher CPB times and cross clamp times; however, no significant differences were observed. The ventilation time was similar between groups, as was the mediastinal tube output at 24 and 48 hours postoperatively. The total number of patients transfused with homologous blood products was observed to be comparable between groups. Patients in the PMEA group received less packed red blood cell (PRBCs) and platelet transfusions intra-operatively than CTR patients; however, no statistical significance was observed. Forty-three percent of patients in the PMEA group were transferred to a step-down unit compared with 33% in the CTR group within the first postoperative day. Overall, there was no significant difference between groups with respect to ICU length of stay. More patients were discharged home within postoperative day four in the PMEA group; however, there was no significant difference.

Platelets

Platelet count was measured at four times: baseline, 30 minutes CPB, P-pump, and 10 minutes post-protamine (Figure 1). Both groups demonstrated similar trends in PLT intraoperatively. Platelets decreased on CPB, rebounded slightly before terminating bypass, and then decreased after protamine administration. There was no significant difference between PMEA and CTR groups. In addition, there was not a statistically significant treatment group by time interaction, which indicates that the group effect does not differ with time.

WBCs

The white blood cell count was measured at three times: baseline, 1 hour CPB, and post-CPB (Figure 2). In the PMEA group, WBC was lower 1 hour on CPB than compared with the CTR group ($6.5 \pm 2.1 \times 10^3$ mcL^{-1} vs. $7.9 \pm 2.6 \times 10^3$ mcL^{-1}). However, WBC were identical between both groups when patients were in the ICU. There was a marginal significant difference between the groups when looking at WBC ($p = 0.041$). In contrast, there was not a statistically significant treatment group by time interaction, which indicates that the group effect does not differ with time.

RBCs

The red blood cell count was measured at three times: baseline, 1 hour CPB, and post-CPB (Figure 3). Both

Table 2. Perioperative patient profiles of the CTR and PMEA groups

	CTR ($n = 30$)	PMEA ($n = 30$)	p Value
CPB time (min)	118.5 ± 33.7	134.1 ± 31.9	NS
Cross clamp time (min)	73.7 ± 21.6	83.9 ± 21.3	NS
Ventilation time (h)			
<4 h	7 (23%)	7 (23%)	NS
4–6 h	15 (50%)	10 (33%)	
6–10 h	5 (17%)	6 (20%)	
≥10 h	3 (10%)	7 (23%)	
Mediastinal tube output (mL)			
MT output–first 24 h	523.2 ± 205.0	562.1 ± 218.2	NS
MT output–second 24 h	346.0 ± 186.7	367.2 ± 145.1	NS
Blood products (u)–48 h postoperative procedure			
Operative PRBC			
0	21 (70%)	23 (77%)	NS
>0	9 (30%)	7 (23%)	
Operative Plt			
0	24 (80%)	26 (87%)	NS
>0	6 (20%)	4 (13%)	
Postoperative PRBC			
0	23 (77%)	21 (70%)	NS
>0	7 (23%)	9 (30%)	
Postoperative Plt			
0	28 (93%)	25 (83%)	NS
>0	2 (7%)	5 (17%)	
Total heparin	43,067 ± 9,359	43,767 ± 9,598	NS
ICU length of stay (days)			
≤1	10 (33%)	13 (43%)	NS
1–2	14 (47%)	12 (40%)	
>2	6 (20%)	5 (17%)	
Hospital length of stay (days)			
≤4	3 (10%)	9 (30%)	NS
4–6	22 (73%)	16 (53%)	
>6	5 (17%)	5 (17%)	
Mortality	0 (0%)	0 (0%)	NS

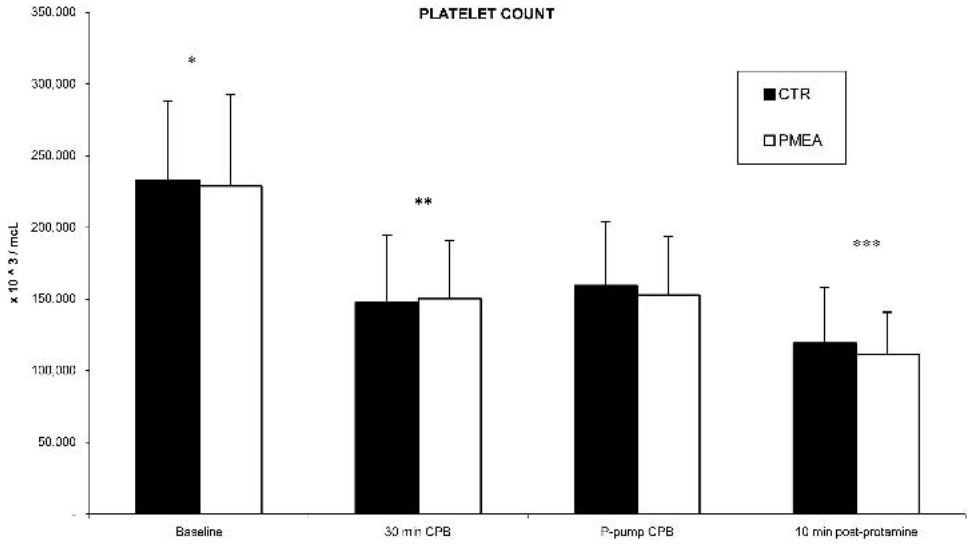

Figure 1. PLT compared between PMEA and CTR groups. Platelets differed significantly over time ($p < 0.001$). *Baseline PLT vs. all the other times ($p < 0.001$). **30 min CPB vs. baseline and 10 min post-protamine ($p < 0.001$). ***10 min post-protamine PLT vs. all other times ($p < 0.001$). P-pump: during proximal anastomoses, before termination of CPB.

groups demonstrated similar trends with respect to RBC levels at the three measured times. In the PMEA group, RBC levels decreased from baseline ($4.8 \pm 0.5 \times 10^6$ mcL^{-1}) to $3.0 \pm 0.3 \times 10^6$ mcL^{-1} on CPB, and then increased to $4.0 \pm 0.4 \times 10^6$ mcL^{-1} post-CPB. There was not a significant difference between PMEA and CTR groups. In addition, there was not a statistically significant treatment group by time interaction, and therefore the difference between groups did not change with time.

Hct

Hct was measured at three times: baseline, 1 hour CPB, and 10 minute post-protamine (Figure 4). Both groups displayed similar trends with respect to Hct levels at the three measured times. In the PMEA group, Hct levels decreased from baseline ($42.9 \pm 3.0\%$) to $26.6 \pm 2.0\%$, and then increased slightly to $29.8 \pm 2.4\%$ post-CPB. There was not a significant difference between PMEA and CTR groups. In addition, there was not a statistically significant treatment group by time interaction, and therefore the difference between groups did not change with time.

The same difference over time was observed in both the PMEA and CTR groups; therefore, the average difference of the PMEA and CTR groups was reported. The following pairwise comparisons were adjusted for multiple comparisons using Tukey's method. Mean PLT, WBC, RBC, and Hct levels differed significantly over time. Baseline PLT were significantly different from all the other times ($p < 0.001$) (Figure 1). At 30 minutes, CPB was not significantly different from P-pump PLT but was significantly different from baseline and 10 minutes post-protamine (both $p < 0.001$). Ten minutes post-protamine, PLT was significantly different from all other times (all $p < 0.001$). Post-CPB WBC was significantly different from all other

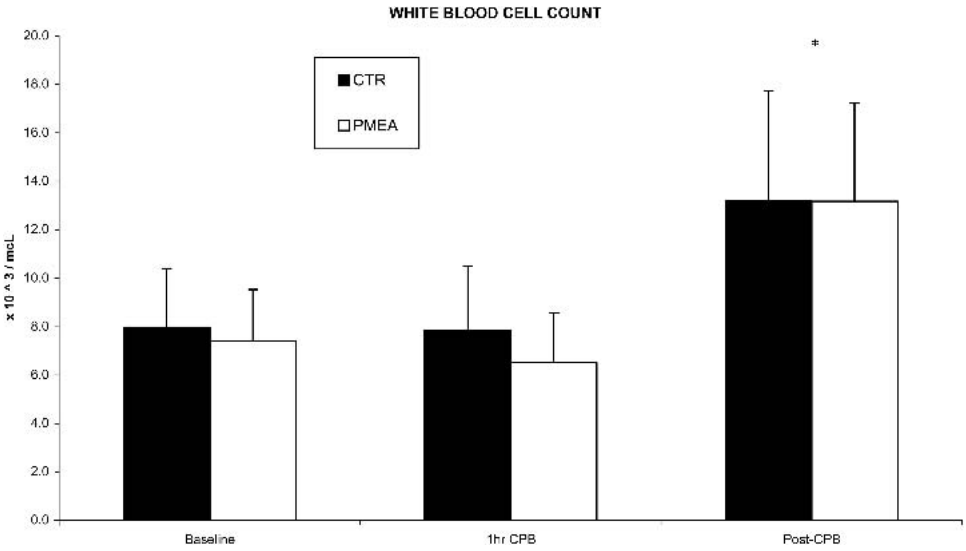

Figure 2. WBCs compared between PMEA and CTR groups. WBC differed significantly over time ($p < 0.001$). *Post-CPB WBC vs. all the other times ($p < 0.001$). Post-CPB: 30 minutes after patients were transported to the ICU.

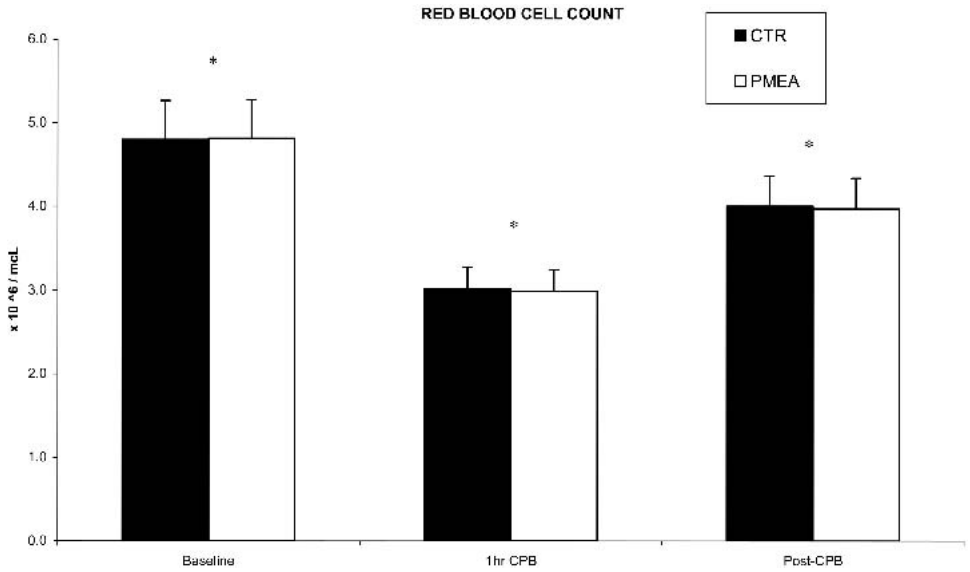

Figure 3. RBCs compared between PMEA and CTR groups. RBCs differed significantly over time ($p < 0.001$). *All time points differed significantly ($p < 0.001$). Post-CPB: 30 minutes after patients were transported to the ICU.

times (all $p < 0.001$) (Figure 2). All time points differed significantly (all $p < 0.001$) for RBC (Figure 3) and Hct (all $p < 0.001$) (Figure 4).

Cost Analysis

Cost data for various departments were compared between the groups with *t* tests (Table 3). The total cost per department represents the amount billed to the patient, which include medications, supplies, and professional fees associated with the hospital. Cost analysis showed marginally higher average costs for patients in the PMEA group. However, there were no statistically significant differences between the groups. Table 4 represents homologous blood product usage in both groups during operative and 48 hours postoperative procedure. In the PMEA group, fewer PRBCs and platelets were used during the operative procedure, and fewer platelets were administered postoperatively as well. Less use of homologous blood products translated to marginal savings of $83.41 in the PMEA group. The average cost for blood products in the CTR group was $299.91 and in the PMEA group was $216.50. The average cost for blood products was not statistically different between the two groups.

DISCUSSION

The advantages of PMEA for biomedical applications have been reported in literature to include blood compatibility, low toxicity, adhesive property, ease to copolymerize, and easiness to control quality. In vitro investigations have shown effectiveness of PMEA toward blood compat-

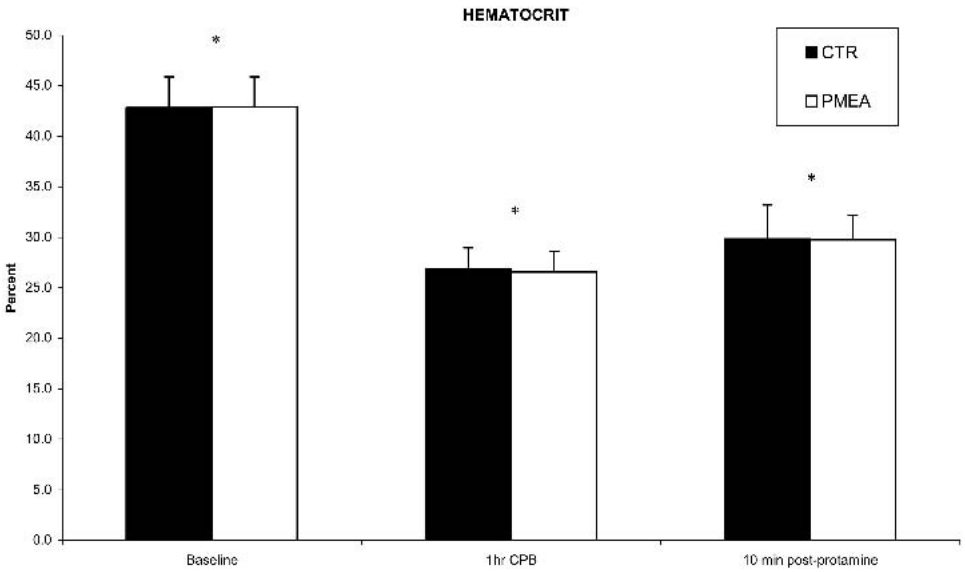

Figure 4. Changes in Hct intraoperatively between PMEA and CTR groups. Hct differs significantly over time ($p < 0.001$). *All time points differed significantly ($p < 0.001$).

Table 3. Comparison of costs for various departments.

	CTR (n = 30)	PMEA (n = 30)	p Value
Anesthesia	1,166.48 ± 187.43	1,231.39 ± 122.08	NS
Intensive care unit	2,728.88 ± 1,177.75	3,028.94 ± 1,693.06	NS
Respiratory therapy	2,369.49 ± 414.52	2,708.73 ± 897.07	NS
Stepdown unit	4,262.37 ± 1,371.55	4,514.07 ± 1,678.41	NS
Surgery	17,467.30 ± 1,377.25	17,632.57 ± 982.49	NS
Average total charge	27,994.50 ± 2,433.42	29,115.69 ± 3,466.75	NS

ibility and implied that the water structure inherent to this coating contributes to the blood compatibility (14,15). Baykut et al. evaluated the biocompatibility of PMEA-coated Terumo Capiox 25 oxygenators to heparin-coated models, and observed that PMEA had the lowest platelet and granulocyte reduction rates (16). In addition, the electron microscopy displayed no cellular deposits on fiber samples from the PMEA-coating. Overall, the authors showed more biocompatible characteristics in the PMEA-coating than heparin coatings.

One of the promising characteristics of PMEA is its low platelet adhesion and low degree of adsorbed protein denaturation. Tanaka et al. were able to demonstrate through their experiments that PMEA surface suppressed platelet adhesion and spreading compared to analogous polymer surfaces (17). When surfaces were precoated with human fibrinogen, the numbers of adhered platelets to PMEA was significantly less than adhesions to other polymers. Greenfield et al. investigated the combination of pharmacological utilization and surface modified circuits during simulated CPB (18). Although TEG results indicated significant effects with the aprotinin only group, there was no synergistic effect with aprotinin in conjunction with PMEA.

Various authors have evaluated the efficacy of PMEA-coated ECC in a porcine model to determine whether PMEA-coating on ECC would reduce complement and leukocyte activation during CPB. Saito et al. showed that plasma bradykinin level and the percentages of CD35-positive monocytes in PMEA group were significantly lowered compared to the uncoated group (19). In addition, they observed that the amount of proteins adsorbed on the PMEA circuits were significantly lower than that on the uncoated circuits. Besides measuring bradykinin levels, PLT, platelet adherence and adsorbed proteins with scanning electron microscopy, Suhara et al. measured the thrombin–antithrombin complex (20). The authors compared PMEA with covalent-bonded heparin coating and no coating. Their data suggested that both PMEA and heparin coatings were beneficial over no coating with respect to platelet preservation, production of bradykinin and thrombin–antithrombin complexes, and reduced surface adsorption of plasma proteins on the oxygenators. There were no significant differences between the two types of coating with respect to the measured parameters. However, there was less adsorbed fibrinogen on the PMEA-coated fibers than on the heparin-coated fibers.

Table 4. Homologous blood product use for the CTR and PMEA groups during and after procedure.

	Operative		48 h Postoperative		Total Units		Cost	
	PRBC	Plt	PRBC	Plt	PRBC	Plt	Total	Average
CTR	23	36	15	30	38	66	$8,997.30	$299.91
PMEA	16	22	19	12	35	34	$6,495.10	$216.50

Despite anecdotes of increasing usage of PMEA-coating across the country, there are few clinical studies that have investigated the efficacy of PMEA. The studies that are available have observed benefits. Gunaydin et al. discovered that WBC counts were altogether lower in patients with PMEA-coated oxygenators during and after CPB (21). Significant differences were observed between groups at 15 minutes post-protamine and the morning of the first postoperative day. Platelet count and fibrinogen levels were higher in the PMEA group with significant differences observed at various times. Microscopic evaluation revealed significantly greater adhesion and aggregation of platelets in the non-PMEA group. In a recent article by Ninomiya et al., the authors observed significantly lower levels of C3a and C3-des-Arg during CPB and postoperatively in the PMEA-coated circuit and oxygenator group vs. the CTR group (22). Polymorphonuclear-elastase levels were significantly better in the PMEA group at one hour post-CPB. Platelet preservation at one hour CPB was significantly better in the PMEA group.

In this evaluation, we focused primarily on how PMEA-coating could be efficacious in terms of clinical parameters. We anticipated PMEA-coating to significantly improve the biocompatility of the ECC; however, our statistical analysis of the data demonstrated otherwise between groups. Despite many of the results not being significantly different, with the exception of WBC, many of the measured parameters were improved for the PMEA group. For example, we observed a trend towards less platelet use operatively and 48 hours postoperatively, which translated to less cost to patients. It was important to note that even though patients had an adequate PLT, patients who expe-

rienced bleeding as determined by the physician, received platelets due to poor platelet function.

In this study, we used the measured values of blood and did not account for hemodilution because Hct values remained similar between groups perioperatively as depicted in Figure 4. Furthermore, as PRBCs transfusion occurred during CPB, it was difficult to calculate a corrected factor for hemodilution. In addition, we noted that patients between 60 to 70 kg were transfused more frequently to maintain a Hct greater than 20%. This trend was noted in both groups, which resulted in similar PRBC transfusions (Table 4). Higher number of females in the CTR group could explain the increased transfusion requirements in this evaluation. In general, women had a lower Hct during bypass than men. Authors such as DeFoe et al. (23) and Cormack et al. (24) found that a low Hct during CPB was associated with increased in-hospital mortality. Women, patients with small body surface areas, and patients who were anemic prior to undergoing CABG were strong predictors of low Hct.

Although both groups were evenly matched in preoperative data, patients in the PMEA group had higher average CPB and cross clamp times. The increased time was attributed to poor target vessels, and therefore surgeons took extra care and time with their anastomoses. This increase in CPB and clamp times may have contributed to the patient's prolonged mechanical ventilation, and therefore extended ICU and hospital lengths of stay. Prolonged CPB times may have also affected platelet count and function, since prolonged exposure to the ECC results in further adsorption of proteins and platelet denaturation.

The use of cardiotomy suction and the contact of blood with air have been investigated in cardiac surgery with CPB. Recycling shed blood with cardiotomy suction is associated with hemolysis, a systemic inflammatory response, impaired hemostasis, and is a source of cerebral fat microemboli (25–27). The use of cardiotomy suction increased WBC in both groups. However, the use of PMEA coating demonstrated a significant difference between the PMEA and CTR groups with respect to WBC ($p = 0.041$). In addition, WBC was observed to be lower at 1 hour CPB.

This evaluation has several limitations. Because of financial issues, we were unable to measure direct markers of inflammation and complement activation. In addition to PLT, we would have liked to measure platelet function, and platelet adsorption with microscopy. Priming with albumin may have delayed and/or reduced fibrinogen adsorption and thereby reduced activation and adhesion of platelets. Precoating the ECC prior to initiating CPB may have contributed to the similar trends in PLT in both groups. In a recent article by Nutter et al., the authors examined the effects of PMEA on coagulation and inflammation under various prime conditions in a modified in vitro CPB circuit (28). The CTR groups showed a significant decline of β-thromboglobulin, interleukin-8, and C3a where albumin was used as a prime component in comparison to just using crystalloid. Overall, albumin had the greatest coagulation preservation in comparison to crystalloid and hetastarch in both CTR and PMEA groups. Another factor that contributed to similar PLT was the PMEA-coated arterial filter in the CTR group. In retrospect, perhaps incorporating two additional groups, a CTR group with no albumin in the prime and a PMEA group without albumin in the prime may have helped to clarify this matter. Finally, because of the fact that our evaluation contained relatively large standard deviations, a larger sample size was necessary to reduce variability in the data.

A power analysis was used to determine the sample size necessary to detect a difference given the effect size for the comparison of PMEA to CTR. The full repeated-measures analysis of variance model was used to determine the effect size for the analysis. When looking at platelets, there was only 21% power to detect the observed difference between PMEA and CTR groups. One hundred eighty patients per group would be required to have 80% power to detect this small of a difference. When looking at RBC, there was only 6% power to detect the observed difference between PMEA and CTR groups. More than 1000 patients per group would be required to have 62% power to detect this small of a difference. When looking at Hct, there was only 11% power to detect the observed difference between PMEA and CTR groups. Four hundred patients per group would be required to have 80% power to detect this small of a difference.

PMEA coating must be purchased at a greater cost than conventional circuits. Currently at our institution, the decision to upgrade to PMEA-coating involves a mark-up in price. In today's increasingly cost-effective hospital environment, it is important to determine whether new advancements in surface modification used with ECC are worth the extra cost and, therefore, will it make up differences with improved patient care. From a cost perspective, it seems that PMEA-coating is not cost-effective as determined by marginally higher average cost for various departments in the PMEA group. One explanation for increased cost may have been patient complications due to risk factors. Although not statistically significant with respect to preoperative risk factors, patients in the PMEA group had higher diabetes mellitus, hyperlipidemia, and hypertension. This may have contributed to the overall cost of patients' recovery as reflected by higher cost in ICU and step-down unit care, and therefore extended patients' hospital length of stay.

Our decision to upgrade to PMEA-coating will not be based on this evaluation alone. The authors believe that coated circuits, whether heparin-coated, surface-modify-

ing additives or PMEA, are the trend towards an improvement in biocompatibility. Despite the technical advancements made to improve the biocompatibility of extracorporeal components, activation of plasma proteins and blood components still occur. The ultimate endeavor remains to be achieved, i.e., the creation of an optimally endothelium-like surface, which blood components would recognize as physiological. The effort to improve biomaterials and to control or eliminate the adverse effects of blood biomaterial interaction remains an active area of extracorporeal research.

In summary, the use of PMEA-coating was observed to improve biocompatibility with respect to PLT and WBC. Although most of the results were not statistically significant, more patients in the PMEA group were transferred to a step-down unit within one day post-procedure and were discharged home within postoperative day 4. In addition, lower transfusions were observed in the PMEA group. The results of this study may help to demonstrate the effectiveness of PMEA coating in lessening the inflammatory response during CPB, preservation of platelets during CPB, and reduction of homologous blood products perioperatively. Further clinical studies are required to thoroughly evaluate the effectiveness of PMEA coating.

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REFERENCES

1. Courtney JM, Matata BM, Yin HQ, Esposito A, Mahiout A. The influence of biomaterials on inflammatory responses to cardiopulmonary bypass. Perfusion. 1996;11:220–8.
2. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 1993;55:552–9.
3. van Oeveren W, Wildevuur RH, Kazatchkine MD. Bio-compatibility of extracorporeal circuits in heart surgery. Transfus Sci. 1990;11: 5–33.
4. Janvier G, Baquey C, Roth C, Benillan N, Belisle S, Hardy JF. Extracorporeal circulation, hemocompatibility, and biomaterials. Ann Thorac Surg. 1996;62:1916–34.
5. Wendel HP, Ziemer G. Coating-techniques to improve the hemocompatibility of artificial devices used for extracorporeal circulation. Eur J Cardiothorac Surg. 1999;16:342–50.
6. Steinberg JB, Kapelanski DP, Olson JD, Weiler JM. Cytokine and complement levels in patients undergoing cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1993;106:1008–16.
7. Jansen PG, te Velthuis H, Huybregts RA, et al. reduced complement activation and improved performance after cardiopulmonary bypass with heparin-coated circuits. J Thorac Cardiovasc Surg. 1995;110: 829–34.
8. Annich GM, Meinhardt JP, Mowery KA, et al. Reduced platelet activation and thrombosis in extracorporeal circuits coated with nitric oxide release polymers. Crit Care Med. 2000;28:915–20.
9. Shimamoto A, Shinji K, Kazua F, et al. Biocompatibility of silicone-coated oxygenators in cardiopulmonary bypass. Ann thorac Surg. 2000;69:115–20.
10. Gu YJ, Boonstra PW, Rijnsburger AA, Haan J, van Oeveren W. Cardiopulmonary bypass circuits treated with surface-modifying additives: a clinical evaluation of blood compatibility. Ann Thorac Surg. 1998;65:1342–7.
11. De Somer F, Francois K, van Oeveren W, et al. Phosphorylcholine coating of extracorporeal circuits provides natural protection against blood activation by the material surface. Eur J Cardiothorac Surg. 2000;18:602–6.
12. Tanaka M, Motomura T, Kawada M, et al. Blood compatible aspects of poly(2-methoxyethylacrylate) (PMEA)-relationship between protein adsorption and platelet adhesion on PMEA surface. Biomaterials. 2000;21:1471–81.
13. Suhara H, Sawa Y, Motonobu N, et al. Efficacy of a new coating material, PMEA, for cardiopulmonary bypass circuits in a porcine model. Ann Thorac Surg. 2001;71:1603–8.
14. Tanaka M, Motomura T, Ishii N, et al. Cold crystallization of water in hydrated poly(2-methoxyethyl acrylate) (PMEA). Polym Int. 2000;49:1709–13.
15. Tanaka M, Mochizuki A, Ishii N, Motomura T, Hatakeyama T. Study of blood compatibility with poly(2-methoxyethyl acrylate). Relationship between water structure and platelet compatibility in poly(2-methoxyethylacrylate-co-2-hydroxyethylmethacrylate). Biomacromolecules. 2002;3:36–41.
16. Baykut D, Bernet F, Wehrle J, Weichelt K, Schwartz P, Zerkowski HR. New surface biopolymers for oxygenators: an in vitro hemocompatibility test of poly(2-methoxyethylacrylate). Eur J Med Res. 2001;6:297–305.
17. Tanaka M, Motomura T, Kawada M, et al. Blood compatible aspects of poly(2-methoxyethylacrylate) (PMEA)-relationship between protein adsorption and platelet adhesion on PMEA surface. Biomaterials. 2000;21:1471–81.
18. Greenfield BL, Brinkman KR, Koziol KL, et al. The effect of surface modification and aprotinin on cellular injury simulated cardiopulmonary bypass. J Extra Corpor Technol. 2002;34:267–70.
19. Saito N, Motoyama S, Sawamoto J. Effects of new polymer-coated extracorporeal circuits on biocompatibility during cardiopulmonary bypass. Artif Organs. 2000;24:547–54.
20. Suhara H, Sawa Y, Nishimura M, et al. Efficacy of a new coating material, PMEA, for cardiopulmonary bypass circuits in a porcine model. Ann Thorac Surg. 2001;71:1603–8.
21. Gunaydin S, Farsak B, Kocakulak M, Sari T, Yorgancioglu C, Zorlutuna Y. Clinical performance and biocompatibility of poly(2-methoxyethylacrylate)-coated extracorporeal circuits. Ann Thorac Surg. 2002;74:819–24.
22. Ninomiya M, Miyaji K, Takamoto S. Influence of PMEA-coated bypass circuits on perioperative inflammatory response. Ann Thorac Surg. 2003;75:913–8.
23. DeFoe GR, Ross CS, Olmstead EM, et al. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. Ann Thorac Surg. 2001;71:769–76.
24. Cormack JE, Forest RJ, Groom RC, Morton J. Size makes a difference: Use of a low-prime cardiopulmonary bypass circuit and autologous priming in small adults. Perfusion. 2000;15:129–35.
25. Jewell AE, Akowuah EF, Suvarna SK, Braidley P, Hopkinson D, Cooper G. A prospective randomized comparison of cardiotomy suction and cell saver for recycling shed blood during cardiac surgery. Eur J Cardiothorac Surg. 2003;23:633–6.
26. Spanier T, Tector K, Schwartz G, et al. Endotoxin in pooled pericardial blood contributes to the systemic inflammatory response during cardiac surgery. Perfusion. 2000;15:427–31.
27. Pierangeli A, Masieri V, Bruzzi F, et al. Haemolysis during cardiopulmonary bypass: how to reduce the free haemoglobin by managing the suctioned blood separately. Perfusion. 2001;16:519–24.
28. Nutter BT, Stammers AH, Schmer RG, et al. The rheological effects of X-coating™ with albumin and hetastarch on blood during cardiopulmonary bypass. J Extra Corpor Technol. 2004;36:36–43.