Original Article

Quantitative Evaluation of Heparin-Coated versus Non–Heparin-Coated Bypass Circuits During Cardiopulmonary Bypass

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ABSTRACT

The extracorporealization of blood activates various elements of the fibrinolytic, coagulation, and complement systems. It is theorized that advancements in biocompatibility ameliorate many of the changes leading to improved patient management. The purpose of this study was to determine if heparin-coated circuit (HCC) utilization during cardiopulmonary bypass enhances patient outcomes in a cost-effective manner.

A search of the English medical literature was completed to identify all clinical, prospective, randomized trials comparing HCC and non-HCC in patients undergoing coronary artery bypass grafting or valvular surgery. Twenty-six papers consisting of a sample size of 1515 patients were identified and included in the study parameters. The study distinguished between Duraflo II and Carmeda coating techniques and matched papers with different heparin loading doses, as well as use of a heparin-coated cardiotomy. Study parameters were matched for all papers and analyzed according to the availability of data.

Statistically significant benefits of HCC were found in postoperative blood loss, time in the ICU, end bypass C3a, time to extubation, end bypass lactoferrin, and end platelet count, but not with respect to postoperative chest tube drainage, red blood cell transfusions, and end bypass TAT complex, D-dimers, and BTG. Data comparing the use of coated or uncoated cardiotomy utilization failed to demonstrate a benefit to heparin coating. Several immunological variables were ameliorated when Carmeda HCC was utilized, although data were insufficient to establish a cost–benefit analysis. In conclusion, heparin-coated circuitry provided statistically better results when compared to noncoated circuitry.

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INTRODUCTION

Since the advent of cardiac surgery and cardiopulmonary bypass (CPB), clinicians have sought to provide better patient care by using more biocompatible equipment. The use of the extracorporeal bypass circuit has been found to activate the clotting cascade and complement (1, 2). This leads to increased sheer stress, increased platelet adhesion and aggregation, and leukopenia (1–4). These factors alter platelet function, activate clotting factors, and enhance complement activation, which results in increased morbidity and mortality in patients undergoing cardiac surgery (5).

During CPB platelets are continuously activated which causes them to lose their receptor sites and impair hemostatic mechanisms (6). Platelets have been shown to adhere to synthetic surfaces within 1 minute of contact (7). This adhesion then stimulates the coagulation cascade by activating fibrinogen. Fibrinogen is a necessary cofactor for platelet adhesion to surfaces, which also influences aggregation (8). The continuous activation of platelets during CPB exhausts the platelet granule content (9–11) and has been suggested as the main cause of impaired hemostasis (12). By inhibiting the binding of fibrinogen to platelets by heparin or heparin-coated surfaces, less platelet damage will result.

The activation of the coagulation cascade is another detrimental effect as a result of the extracorporeal circuit. All extracorporeal surfaces are thrombogenic, and once fibrin is deposited on the ECC, activation of additional factors continues. As blood passes across the deposited thrombus, turbulence is enhanced, which causes damage and lysis of red blood cells, enhancing patient injury. The coagulation cascade is directly linked to the complement cascade by the factor kallikrein. Inhibition of the coagulation cascade has direct effects on reducing complement activation.

A well-demonstrated method for determining the degree of biocompatibility of the extracorporeal circuit is measuring the degree of complement activation. The anaphylatoxin C3a and C5a are responsible for much of the injury associated with complement activation (13). The generation of these substances causes an increased activation of polymorphonuclear neutrophils, which become trapped within the pulmonary system during and after CPB (14). Complement activation causes significant damage to the lungs by synergistically acting with tissue necrosis factor to upregulate neutrophil CD11b surface expression, which can lead to adult respiratory distress syndrome (15, 16). Complement activation also causes other systemic dysfunction, which can increase post-CPB complications, hospital stay, and cost.

Heparin sodium, a polysaccharide that inhibits the formation of thrombin, is routinely used in extracorporeal circulation (ECC) and has been shown to decrease these adverse effects significantly. Heparin is a molecule that works by binding to antithrombin III and inhibiting coagulation factors IIa, IXa, Xa, XIa, and XIIa (17). This, in turn, obstructs the internal and common pathways of the coagulation cascade (18).

In an attempt to decrease the activation of biological systems resulting from ECC, mechanisms of attaching bioactive molecules to nonendothelialized circuit surfaces have been designed, and these have been used clinically for the past several years. By immobilizing heparin on extracorporeal surfaces, it is hypothesized that this will decrease the amount of anaphylaxis and reperfusion injury caused by the extracorporeal contact with blood.

Biocompatible or heparin-coated circuits have been commercially available since the early 1980s. In the beginning of heparin-coated circuit development, specific parts of the extracorporeal circuit were coated. This included arterial line filters and oxygenators. Later, cannula-to-cannula circuits were developed that included all components of the extracorporeal circuit, except for the cardiotomy reservoir. Finally, cardiotomy reservoirs became coated, which completed the entire circuit.

In today's increasingly cost-effective hospital environment, it is important to see if these different components and treatments used with the biocompatible circuits are worth the extra cost and make up for the difference with improved patient care. The present study was undertaken to determine if patient outcomes were affected by the use of heparin-coated circuits. The two types of biocompatible surfaces that have been analyzed are an ionically bonded formulation (Duraflo II®[a]) and a covalently bonded formulation (Carmeda®[b]).

MATERIALS AND METHODS

When attempting to determine the effectiveness of a treatment in clinical medicine several techniques are available. One of the primary methods is the accumulation of data from prospective, randomized studies, and analyzing them with a test called a meta-analysis. A meta-analysis is a statistical test of a large collection of data resulting from individual studies for the purpose of integrating the findings (19). The meta-analysis is able to quantifiably show direct relationships between variables; whereas, correlation and statistical significant studies cannot always achieve this.

STUDY PARAMETERS

The first step in this process was to identify the specific parameters possibly affecting the heparin-coated treatments. The parameters were identified using the many datapoints each paper presented. Datapoints that were similar between each group were categorized together. Once the data were grouped together, each category was broken down into subdivisions that include presence or absence of heparin coating, type of heparin

a Bentley division, Baxter Healthcare Corp., Irvine, CA 92714
b Medtronic Cardiopulmonary, Anaheim, CA 92807

coating, presence or absence of a heparin-coated cardiotomy, and heparin dose administered to the patient on bypass.

The published studies entry criteria included: clinically, prospective, and randomized trails that compared heparin-coated bypass circuits to nonheparin-coated circuits, adult patients from the age of 19 to the age of 80 undergoing coronary artery bypass grafting (CABG), valvular surgery, or both. The year of each study and gender difference between groups was also noted.

The study matched similar circuit set-ups. These included the ionically bonded circuit, Duraflo II, which is assembled by applying USP porcine heparin with a carrier agent to a synthetic surface, and covalently bonded circuit, Carmeda, which is produced by allocating a fragmented polysaccharide of heparin onto the surface of the extracorporeal circuit. These materials then bind to antithrombin III, causing some inhibition of the coagulation cascade. Cannula-to-cannula coated circuits without a heparin-coated cardiotomy were compared to matching circuits that included a heparin-coated cardiotomy. The heparin administration protocol was distinguished between full heparin loading dose, half loading dose, two-thirds loading dose, one-third loading dose, and one-quarter loading dose.

The parameters that were incorporated into the study were taken from those most frequently mentioned in the literature and included: length of hospital stay, number of blood transfusions, chest tube drainage, length of time in the intensive care unit, amount of blood loss, amount of autotransfusion, packed red blood cells transfused, time to extubate patient, and mortality rates. Other factors noted are the various hematological indicators that include the anaphylatoxin of complement activation (C3a and C3b), platelet count, thrombin–antithrombin complex (TAT), fibrinogen concentration, D-dimers, lactoferrin, the terminal complement complex (TCC), polymorphoneutrophils (PMN), and β-thromboglobulin (BTG). Within these parameters, each datapoint is subdivided further to include the specific time intervals mentioned in each study. Statistical analysis was performed to see the significance of each data group. This was to determine if there is an advantage to one group or another.

LITERATURE SEARCH

A literature search was completed utilizing the electronic databases of Medline®[c] and the Cumulative Index of Nursing and Allied Health Literature (CINAHL)®[d]. The search time line included all sources dated from 1966 to February 1997. Searches of the journal *Perfusion* (pre 1990), the *Proceedings of the American Academy of Cardiovascular Perfusion*, and *The Journal of Extra-Corporeal Technology* (pre 1982) were also included, because they were not listed on either of these databases, and they covered all years of publication.

c Medline, Bethesda, MD 20894
d CINAHL, Glendale, CA 91209

STATISTICS

Confidence Intervals: Ninety-five percent confidence intervals, which acknowledge the varying sample sizes, for the weighted mean differences are presented. These intervals provide an estimate of the variability in the estimated weighted mean difference; specifically, we would expect the true weighted mean difference to be within the interval 95% of the time. Also, when the 95% confidence interval does not include zero, the weighted mean difference would be statistically significantly different from zero at the 0.05 level.

Weighted Means: The results on the various perfusion outcomes are summarized using weighted mean differences. For each study, the difference in the outcome between each category is computed. The weighted mean difference is then computed by combining the study-specific estimated differences and incorporating the variable sample sizes across the studies.

RESULTS

Data for the study were obtained from 26 published reports with a total sample size of 1515 patients. The breakdown of the numbers of the selection criteria is shown in Table 1.

Results of each study were arranged according to the outcome indicators that each study represented. Within these outcome indicators, each study reported results at a variety of time intervals. The time intervals and outcome indicator parameters were matched for statistical review. After analyzing the data, it was determined that a classical meta-analysis statistical format could not be done because of lack of similar data. Instead, the statistics were formatted by using weighted means and analyzed by confidence intervals to show if there was statistical significance or not. Of the categories selected, only those that presented with at least three datapoints, or a sample size greater than 250 patients, were chosen for statistical review.

Table 1: Representation of selection criteria

Treatment type	Reference
Coating	
Duraflo II	16
Carmeda	9
Both	1
Coated cardiotomy in circuit	
With	18
Without	8
Heparin protocol	
Full loading dose	15
¾ Loading dose	3
⅔ Loading dose	1
½ Loading dose	5
⅓ Loading dose	1
¼ Loading dose	1

CONFIDENCE INTERVALS

To verify statistical significance, confidence intervals were used between the HC and NHC groups. Results of the confidence interval tests are summarized in Table 2.

WEIGHTED MEANS

Analyzed comparison of Carmeda versus Duraflo II heparin-coated circuits represented a total sample size that included 776 patients. The results of the comparison are shown in Table 3. Comparisons of length of stay, extubation time, mortality, and intensive care unit time were unavailable between Carmeda and Duraflo II circuits, because none of these variables was reported in the Carmeda data available for the study. Analysis was done on two different set-ups of heparin-coated circuits, one that included a heparin-coated cardiotomy in the circuit versus one without a coated cardiotomy. This analysis also had to be done by weighted means because of the small number of data. The results of the analysis are shown in Table 4. Comparisons of length of stay, 24-hour chest tube drainage, extubation time, and intensive care unit time were unavailable between the coated and the uncoated groups, because variables were missing in one category or the other.

Statistical tests to decide the difference between the five loading doses of heparin were not possible to perform, because of inadequate data representation from all of the groups, except for the full loading dose group, which had more than half of all of the total results.

DISCUSSION

Controversy exists about the effectiveness of using heparin-coated cardiopulmonary bypass circuits in terms of whether or not they do, indeed, improve patient outcomes in cardiac surgery. Some studies have indicated an improvement with the use of these circuits; whereas others have not discovered any significant difference. Heparin-coated circuits were designed to improve patient care by decreasing activation of immunological and hematological factors (3, 4). This was hypothesized to lead to lower post- cardiopulmonary bypass complications and a quicker recovery, which would be expressed in improved outcome indicator measures.

Cost effectiveness has become an important part of health care in the 1990s. Not only is improved patient care a concern, but the cost of providing services to the patient is a factor in determining the scope of practice for perfusion and other specialties. The goal of this study was to take all available information within the selective criteria to make a global assessment on the effectiveness of this treatment option. When compared, heparin-coated circuits showed significantly better results in some of the outcome indicators (which included time in the intensive care unit, postoperative blood loss, end bypass platelet count, and extubation time) to nonheparin-coated circuits. These are the factors that many clinicians look at when determining if a treatment option is successful. By spending less time in the ICU and requiring fewer blood products, the patient and the hospital can save money and avoid potential complications.

Heparin-coated circuits must be purchased at a greater cost than conventional circuits. The Duraflo II coating costs up to 5% more than a non-coated circuit. Carmeda-coated Medtronic tubing packs cost between 70 to 90% more than uncoated tubing packs. It is possible to use a cost analysis profile to determine if either of the circuit coatings provides an improved treatment option that is also cost effective. With the use of confidence intervals, it was demonstrated that heparin-coated circuits have a statistically better result then with nonheparin-coated circuits. A day's stay in the intensive care unit at the

Table 2: Confidence intervals between heparin and nonheparin-coated bypass circuits

Parameter	95% Confidence intervals			Treatment significance	
Total postoperative blood loss	−606.7	−489.2	−371.8	HC	*
End bypass TAT complex	−0.60	+11.8	+24.1		
End bypass D-dimer	−8.1	+13.7	+35.6		
Extubation time	−10.7	−5.9	−1.1	HC	*
ICU time	−22.8	−13.5	−4.1	HC	*
End bypass TCC	−71.9	−56.3	−40.6	HC	*
End bypass BTG	−32.7	−3.50	+25.7		
24-Hour chest tube drainage	−151.3	−66.9	+17.5		
End bypass platelet count	+0.15	+6.5	+12.8	HC	*
PRBCs transfused	−0.77	−0.38	+.0048		
End bypass lactoferrin	−644.2	−436.4	−228.6	HC	*
End bypass C3a	−197.1	+128.0	−58.9	HC	*

BTG = beta thromboglobulin; HC = heparin-coated; ICU = intensive care unit; TAT = thrombin–antithrombin complex.
Statistical significance (*) favored either HC or nonheparin-coated circuits.

Table 3: Comparison of Carmeda and Duraflow II heparin-coated bypass circuits

Parameter	Carmeda	Duraflo II	Sample #
End CPB autotransfusion	456.00 mL	600.93 mL	232
End CPB BTG	220.55 mL	200.77 mL	160
PRBCs Transfused	2.60 units	0.96 units	202
End CPB TAT complex	35.80 μg/L	71.37 μg/L	155
End CPB D- dimers	434.15 ng/mL	812.34 ng/mL	176
Total postoperative blood loss	690.29 mL	646.90 mL	258
End CPB lactoferrin	536.95 μg/L	563.52 μg/L	49
End CPB platelet count	154,770/mL	94,820/mL	270
24-Hour chest tube drainge	780.00 mL	629.82 mL	161
End CPB C3a	690.00 ng/mL	908.00 ng/mL	80

BTG = beta thromboglobulin; CPB = cardiopulmonary bypass; TAT = thrombin–antithrombin complex

Table 4: Comparison of heparin-coated bypass circuits using either a heparin-coated cardiotomy or an uncoated cardiotomy

Parameter	Coated	Uncoated	Sample #
End CPB autotransfusion	600.93 mL	456.00 mL	232
End CPB BTG	202.46 mL	215.00 mL	160
PRBCs transfused	0.96 units	2.60 units	202
End CPB TAT complex	70.01 μg/L	20.00 μg/L	155
End CPB D- dimers	760.30 ng/mL	650.90 ng/mL	176
Total postoperative blood loss	643.40 mL	694.35 mL	258
End CPB lactoferrin	533.69 μg/L	659.00 μg/L	49
End CPB platelet count	104,560/mL	200.20/mL	270
Mortality	0.02%	0.00%	318
End CPB C3a	439.25 ng/mL	1440.00 ng/mL	80

BTG = beta thromboglobulin; CPB = cardiopulmonary bypass; TAT = thrombin–antithrombin complex

University of Nebraska Medical Center costs $865.00. A tubing pack from cannula-to-cannula without autotransfusion at the University of Nebraska Medical Center costs $600.00. When adding the extra 5% that the Duraflo II coating costs and subtracting the time and money saved in the intensive care unit, the Duraflo II heparin-coated circuits do provide a cost-effective means of improving patient care than without heparin-coated circuitry. Because there are no data on intensive care unit stay with the Carmeda group, a cost analysis profile could not be done.

Upon reviewing the literature, different types of heparin coatings, different anticoagulation schemes, and the presence or absence of a heparin-coated cardiotomy within the circuit have all demonstrated mixed results. It was the intent of this study to demonstrate statistically which of these treatment options would provide better and cost- effective results. However, small numbers of similar data within these categories left us unable to perform confidence intervals to prove statistical significance. Instead, weighted means were used to provide a comparison of each option.

Analyzing the available data between the Carmeda heparin-coated circuits and the Duraflo II heparin-coated circuits using weighted means indicate that the Carmeda coated circuits showed reductions in end cardiopulmonary bypass autotransfusion, D-dimer levels, TAT complex levels, lactoferrin, C3a, and a higher platelet count. Duraflo II heparin-coated circuits had lower postoperative blood loss, 24-h chest tube drainage, packed red blood cells transfused, and BTG levels. These numbers suggest that immunological factors were maintained better with the use of the Carmeda coated circuits. Hematological factors, excluding platelet count, advocate that the Duraflo II heparin coating provides improved results.

Comparison between uncoated and coated cardiotomy groups found that the coated cardiotomy group had lower amounts of BTG, PRBCs transfused, postoperative blood loss, lactoferrin, and C3a. The uncoated cardiotomy group had lower TAT complex, D-dimers, higher platelet counts, and lower mortality rates. These data suggest that the coated cardiotomy group did not have as overwhelming an advantage as might have been expected. Because cardiotomy reservoirs are

an open system to air, there is the possibility that the effectiveness of heparin coating in these devices is negated.

Literature on the amount of heparin loading dose used with heparin-coated circuits has yielded mixed reviews. The concept is that, with the extra heparin found in the circuit, activated clotting times can be reduced and bypass maintained at a safe level. It is the reduction in heparin that is theorized to cause less hematological problems during and after cardiac surgery. Because of the unorthodox results with the number of samples reported with each heparin-loading dose, comparison between each of the loading doses was not possible.

In this study, the use of heparin-coated bypass circuits have shown statistically better results than similar noncoated circuits by decreasing hospital and patient costs attributable to less time in the intensive care unit and fewer complications. From a cost prospective, it seems that the Duraflo II circuits were comparable to the more expensive Carmeda circuits with the weighted means that were available. Surprisingly, coating of the cardiotomy reservoir in the heparin-coated group did not demonstrate improved results over similar circuits without a coated reservoir.

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