Use of Electron-Beam Sterilized Hemodialysis Membranes and Risk of Thrombocytopenia

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Context Thrombocytopenia is not widely recognized as a potential dialyzer-related complication. Following the observation of significant thrombocytopenia among 20 patients undergoing hemodialysis in a single dialysis unit after the introduction of dialyzers sterilized by electron beam (e-beam), a larger investigation was undertaken.

Objective To determine the prevalence and etiology of thrombocytopenia in hemodialysis populations of 2 Canadian provinces (British Columbia and Alberta).

Design, Setting, and Participants A cohort study of patients undergoing hemodialysis in British Columbia (n=1706) and southern Alberta (n=425) between April 1, 2009, and November 30, 2010. Retrospective analyses of historical patient, laboratory, and dialyzer data predating conversion to e-beam dialyzers were undertaken, with prospective collection of predialysis and postdialysis platelet counts before and after the change from e-beam to non–e-beam sterilized dialyzers in September 2009.

Main Outcome Measure Significant thrombocytopenia, defined a priori as postdialysis treatment platelet count of less than 100×10^3/μL and a postdialysis decrease in platelet count of more than 15%.

Results Among 1706 patients undergoing hemodialysis in British Columbia, 1411 (83%) were undergoing hemodialysis with e-beam sterilized dialyzers. Of 1706 patients, 194 (11.4%; 95% CI, 9.9%-12.9%) had postdialysis platelet counts of less than 100×10^3/μL; 400 (23.4%; 95% CI, 21.5%-25.5%) had postdialysis decreases in platelet counts of more than 15%; and 123 (7.2%; 95% CI, 6.0%-8.6%) met both criteria. Among 425 patients in Alberta undergoing dialysis with polysulfone, e-beam sterilized dialyzers made by a different manufacturer, 46 (10.8%; 95% CI, 8.1%-14.3%) had platelet counts of less than 100×10^3/μL; 156 (32.0%; 95% CI, 27.6%-36.7%) had decreases in platelet counts of more than 15%; and 31 (7.3%; 95% CI, 5.1%-10.3%) met both criteria. In multivariable analysis adjusting for patient and dialysis history characteristics, a significant association was observed between using an e-beam sterilized dialyzer and risk of significant thrombocytopenia (odds ratio [OR], 2.52; 95% CI, 1.20-5.29; $P=.02$). Compared with use of e-beam sterilized dialyzers, following the change to use of non–e-beam sterilized dialyzers, among 1784 patients, significant reductions were observed in postdialysis thrombocytopenia (120 patients [6.7%; 95% CI, 5.6%-8.0%; $P<.001$] had platelet counts of $<100\times10^3$/μL; 167 patients [9.4%; 95% CI, 8.1%-10.8%; $P<.001$] had decreases in platelet counts of >15%; and 38 patients [2.1%; 95% CI, 1.5%-2.9%; $P<.001$] met both criteria). Using generalized estimating equation modeling for repeated data with binary outcome, after adjusting for patient characteristics, the odds of significant thrombocytopenia were higher during the use of e-beam sterilized dialyzers than with use of non–e-beam sterilized dialyzers (OR, 3.57; 95% CI, 2.54-5.04; $P<.001$).

Conclusion In this cohort of patients undergoing hemodialysis in 2 Canadian provinces in 2009-2010, the use of e-beam sterilized dialyzers was associated with significant thrombocytopenia following dialysis.

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Adverse device reactions to hemodialysis treatments are uncommon but can still occur in today's era of hemodialysis membranes and technology. During hemodialysis treatment, patients are exposed to a variety of components of the dialysis circuit and could have an adverse reaction to blood tubing, dialyzer membranes, and dialysis solutions. Although some adverse reactions are immediately clinically apparent, other reactions may have more subtle manifestations.

Historically, thrombocytopenia related to hemodialysis treatments was used as a measure of dialyzer membrane biocompatibility, dating back to the use of nonsynthetic membrane materials, which had the potential to activate the inflammatory cascade or have adverse effects on platelet function or number.[1] With the synthetic and highly biocompatible dialyzer membranes in use today, these effects are uncommon; therefore, thrombocytopenia occurring among patients undergoing hemodialysis usually is attributed to other causes, such as medications, immune-related disorders, or sepsis.

Standard clinical practice in dialysis units involves drawing complete blood work predialysis (before initiation of hemodialysis) to monitor biochemical markers including blood cell counts, and only a urea level postdialysis (after completion of hemodialysis) to measure urea clearance. It is not routine to obtain postdialysis blood cell count measurements. Therefore, iden-

For editorial comment see p 1707.

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tification of postdialysis thrombocytopenia would be difficult in standard clinical practice.

We describe the occurrence of profound thrombocytopenia, first identified in an index case and subsequently observed in multiple patients receiving hemodialysis at our dialysis unit that appeared associated with the introduction of electron beam (e-beam) sterilized dialyzer membranes. These cases prompted a region-wide investigation to determine the prevalence and etiology of thrombocytopenia in hemodialysis populations of 2 Canadian provinces (British Columbia and Alberta).

METHODS

Index Case

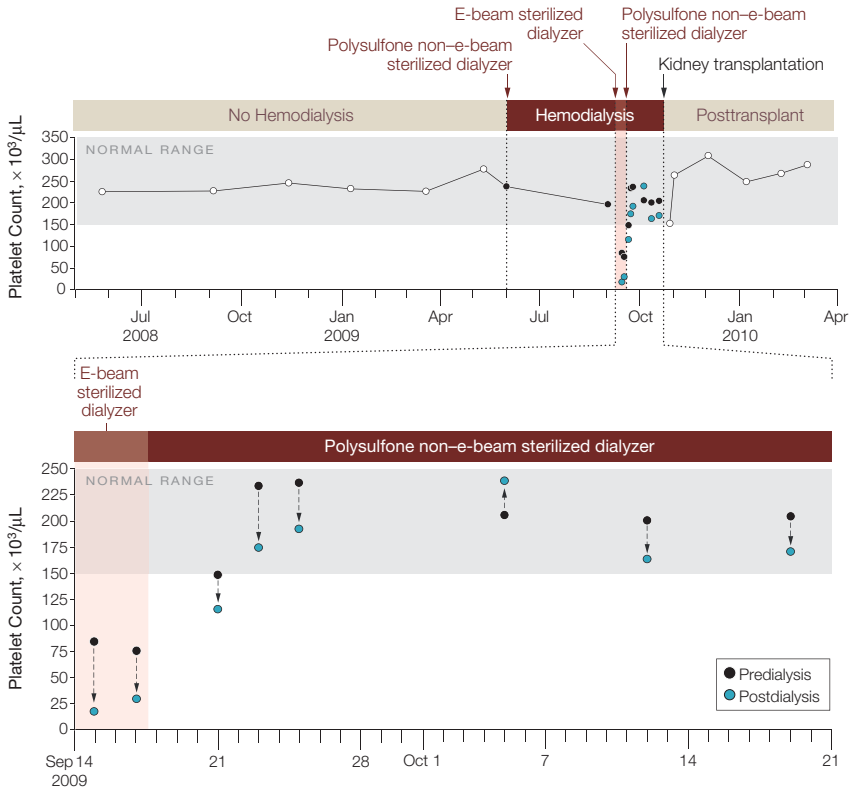
The index case was a 51-year-old woman with end-stage renal disease secondary to polycystic kidney disease and a history of congenital heart disease (tetralogy of Fallot), hypertension, and quiescent lupus. She had been undergoing hemodialysis since June 2009 using a polysulfone, gamma-radiation sterilized dialyzer and had usual platelet counts ranging between 197×10^3/μL and 278×10^3/μL. In September 2009, the dialysis unit switched to the use of a polysulfone e-beam sterilized dialyzer.

On September 15, 2009, the patient was admitted for a scheduled kidney transplant and admission blood work revealed a platelet count of 80×10^3/μL, white blood cell (WBC) count of 5300/μL, and hemoglobin level of 125 g/L. The patient underwent regularly scheduled dialysis using the polysulfone e-beam sterilized dialyzer. Her platelet count obtained following dialysis was 18×10^3/μL (with a WBC count of 11 300/μL and hemoglobin level of 114 g/L). Due to the significant and unexplained thrombocytopenia, her kidney transplant was canceled and further diagnostic workup and management ensued.

Platelet counts obtained before and after subsequent dialysis performed on September 17, 2009, again revealed a significant decrease from the predialysis to the postdialysis values (FIGURE 1). Heparin anticoagulation was not administered during subsequent dialysis sessions. An extensive workup (TABLE 1), including review of all medications and bone marrow biopsy, revealed no apparent etiology for the thrombocytopenia.

In the absence of other identifiable contributing factors, the possibility of dialyzer-related reaction was raised. On September 19, 2009, the patient's dialyzer was switched to a nonpolysulfone, gamma-radiation sterilized dialyzer and subsequent predialysis platelet counts returned to normal values, with no further significant decreases in postdialysis platelet counts (Figure 1). The patient underwent renal transplant surgery on October 23, 2009, and posttransplant platelet counts have ranged between 241×10^3/μL and 357×10^3/μL, with follow-up through March 4, 2010.

Figure 1. Platelet Count Data for Index Case Patient According to Exposure to Different Dialyzer Membranes



E-beam indicates electron beam. Patient received a successful transplant on October 23, 2009.

Additional Index Cases

Subsequent investigation within the dialysis unit revealed 19 additional patients (eTable 1, available at http://www.jama.com) with dialysis-associated thrombocytopenia, which similarly resolved with changing of the dialysis membrane. All 20 initial index patients developed significant thrombocytopenia after exposure to a polysulfone, e-beam sterilized dialyzer. None of the index patients demonstrated postdialysis thrombocytopenia after hemodialysis was performed using non–e-beam dialyzers (eTable 1). In addition, 2 patients who had recovered their platelet counts after being switched to a non–e-beam sterilized dialyzer were inadvertently reexposed to an e-beam sterilized dialyzer. In these patients, predialysis and postdialysis platelet count measurements confirmed a second occurrence of thrombocytopenia (eFigure 1 and eFigure 2).

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Assessment of all 20 index patients included a review of medications that could cause thrombocytopenia and any medications that potentially could contribute to thrombocytopenia (eg, quinine or heparin) were discontinued. No evidence of insufficient anticoagulation was detected when dialysis blood tubing, arterial and venous chambers, and dialyzer membranes were examined as per routine clinical dialysis practice. Blood work was repeated several times using EDTA blood tubes thereby eliminating the possibility of pseudothrombocytopenia. Only 1 patient had overt bleeding (hemoptysis) and 2 patients had delays of important procedures (transplant and coronary angiography). No patients reported excess bruising and none had evidence of petechiae.

Two dialyzers that had been used during dialysis in 2 of the initial index patients were dismantled. Each dialyzer membrane was evaluated under light microscopy by a hematopathologist. There was abundant clumping of platelets and red blood cells on the dialyzer membrane. Further assessment using electron microscopy was deemed to be of limited value and therefore was not pursued further. Platelet-specific antibodies and activating factors were ordered but due to requirements for special laboratory testing and funding results were not available.

After ruling out other possibilities, we noticed that the first cases of thrombocytopenia related to dialysis had occurred after the introduction of e-beam sterilized dialyzers in our dialysis unit. This observation prompted a more thorough evaluation of the hypothesis that use of the e-beam sterilized dialyzers was associated with thrombocytopenia.

Population and Context

British Columbia, Canada, is a province of 4.2 million people with a large dialysis population served by 37 dialysis units (11 hospital in-center units and 26 community units), home hemodialysis, and peritoneal dialysis. All kidney patient data are housed in a robust information system (patient registration and outcome management information system [PROMIS]) that has laboratory and hospital interfaces permitting large amounts of data capture, which are used for monitoring, quality assurance, and safety purposes. PROMIS also captures data on demographics, medications, and modality details of all renal patients in the province.

Before September 2009, various types of dialyzers were in use across 5 geographically distinct health authorities (eTable 2). After a formal tender process (defined by provincial standards of best practices for contract negotiation), which included requests for proposals and vetting of proposals by business, finance, and content experts, within each region, a provincial dialyzer contract was awarded. This provincial contract guaranteed a minimum of 80% usage of a specific dialyzer (polysulfone, e-beam sterilized) provincially by September 2009.

Southern Alberta has a large dialysis-based population of which the majority (n=425) are within the Calgary region. Patient and laboratory data are captured in the Province of Alberta Renal Information System (PARIS) database and used for monitoring and quality assurance purposes. A nonpolysulfone (AN-69), gamma-radiation sterilized dialyzer was in use before 2008. In 2008, a new dialyzer contract for the southern Alberta region led to a switch to a polysulfone gamma-radiation sterilized dialyzer. In 2009, the same manufacturer introduced a different dialyzer, which was also polysulfone based but e-beam sterilized. In January 2009, all patients in Southern Alberta Renal Program were switched to this new e-beam sterilized dialyzer. Although the 2 dialyzers used in both British Columbia and southern Alberta share similar features (polysulfone, e-beam sterilized), they are manufactured by 2 different companies.

All dialyzers are manufactured and sterilized before shipment to dialysis units for single use. A patient prescribed 1 type of dialyzer remains using the same type of dialyzer for each dialysis treatment.

Table 1. Summary of Diagnostic Workup of Thrombocytopenia in Index Case Patient

Parameter	Finding or Value (Normal Range)
HIT assay[a]	Negative (negative)
Complement levels, g/L	
C3	0.89 (0.90-1.90)
C4	0.18 (0.13-0.46)
Anti-DNA antibody, IU/mL	47 (0-200)
Serum vitamin B_{12} level, pmol/L	362 (156-672)
Red blood cell folate, nmol/L	2132 (>634)
International normalized ratio	1.0 (0.9-1.2)
Partial thromboplastin time, s	29 (24-40)
Fibrinogen, g/L	4.0 (1.5-4.5)
D-dimer, μg/L FEU	2172 (<500)
Lactate dehydrogenase, U/L	211 (115-230)
Bone marrow biopsy	Nondiagnostic

Abbreviations: HIT, heparin-induced thrombocytopenia; FEU, fibrinogen equivalent unit.
SI conversions: To convert serum vitamin B_{12} to pg/mL, divide by 0.7378; red blood cell folate to ng/mL, divide by 2.266.
[a] HIT gel assay tests for the presence of anti-PF4 antibodies; results repeated 3 times.

Review of the study was waived by the Provincial Health Services Authority, who determined that this project was exempt from institutional review board review because it was a patient safety and risk management issue. In the context of applied research and best practices, the Provincial Health Services Authority approved the study for publication. Informed consent was waived at participating institutions because of the use of deidentified data.

Study Design

The study was designed to investigate the hypothesis that postdialysis thrombocytopenia was associated with the change in dialyzers. First, available historical data were examined on average predialysis platelet counts before and after the switch to e-beam dialyzers in both the British Columbia and southern Alberta hemodialysis populations. For British Columbia, province-wide data (including laboratory results obtained every 4-6 weeks as per routine practice) dating back to 6 months before the switch in type of dialyzer were examined (eFigure 3). For southern Alberta data, records dating back to 3

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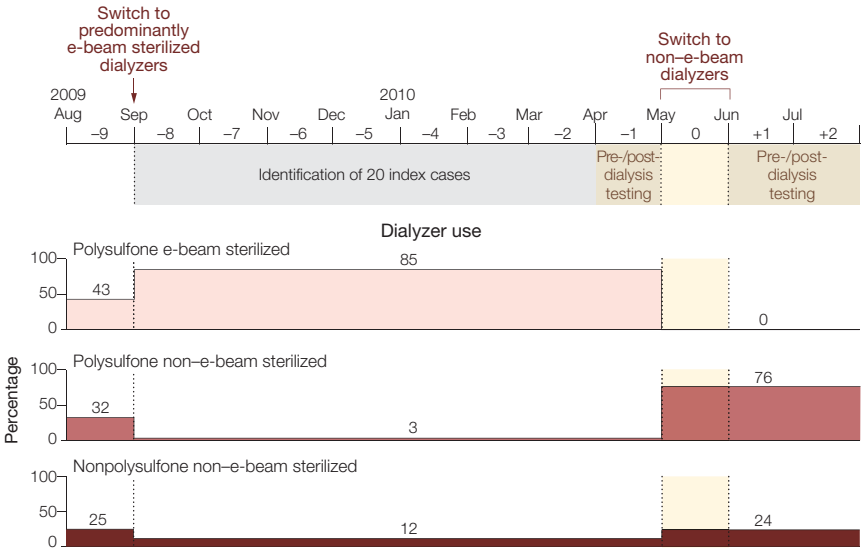
Figure 2. Key Time Points and Distribution of Dialyzers at Each Time Point in British Columbia



E-beam indicates electron beam.

years before the switch to e-beam dialyzers were examined.

Second, prospective measurements of predialysis and postdialysis platelet counts were undertaken in both populations to determine the point prevalence of dialysis-associated thrombocytopenia (month –1) (FIGURE 2). Thereafter, data and clinical patient information were analyzed to identify potential associations between the observed phenomenon of thrombocytopenia and measurable variables. This identified a significant signal between thrombocytopenia and e-beam sterilization, prompting an intervention.

Third, in May 2010 (month 0) (Figure 2) all patients were switched from use of e-beam to non–e-beam sterilized dialyzers. These non–e-beam sterilized dialyzers were ordered from the same manufacturer as part of a contingency within the contract. Prospective predialysis and postdialysis platelet counts were obtained in June/July 2010 (month +1/2) (Figure 2), when the conversion to non–e-beam sterilized dialyzers was complete, to assess the association between change in type of dialyzer and dialysis-associated thrombocytopenia (Figure 2).

Assessment and Definition of Thrombocytopenia

Through physician-driven consensus, predetermined criteria for detection of significant thrombocytopenia were established as the combination of both postdialysis platelet count of less than $100 \times 10^3/\mu L$ and postdialysis platelet count decrease of more than 15% compared with predialysis values; however, evaluation of each criterion alone was also considered and is presented. Based on previous literature, a biocompatible dialyzer can produce a decrease in platelet count of 7% to 9%.[1] Thus, a 15% decrease in the platelet count could identify dialysis-related thrombocytopenia. In addition, given that the normal lower range of platelet count is $150 \times 10^3/\mu L$, a value of less than $100 \times 10^3/\mu L$ would be clinically important.

The rationale for examining a combined outcome of both a decrease in platelet count of at least 15% and an absolute platelet count of less than $100 \times 10^3/\mu L$ was to capture the occurrence of patients with thrombocytopenia who were at highest risk of clinical morbidity, mortality, or both (eg, a 15% decrease in platelet count from an initial value of $375 \times 10^3/\mu L$ would not generally warrant the same clinical concerns compared with a 15% decrease if the initial platelet count was lower). All definitions were established before the start of data collection.

All platelet counts were performed in local accredited laboratories with no changes in methods or apparatus during the time of investigation. Predialysis and postdialysis platelet counts were measured during routine blood work. We endeavored to collect serial blood work after the change in types of dialyzers for a 6-month period. Laboratory test results were obtained from 80% of patients with dialysis. Reasons for lack of complete collection included hospitalization and receipt of dialysis at home or in remote areas, both of which limited access to blood work.

Statistical Analysis

Descriptive statistics are shown as mean (standard deviation) or median (interquartile range), depending on the underlying distribution. Continuous and categorical variables were compared using *t* test or Wilcoxon rank sum test and χ^2 tests, respectively. We used analysis of variance and χ^2 tests to compare between 3 groups (patients who were undergoing dialysis with non–e-beam dialyzers vs patients who were undergoing dialysis with e-beam dialyzers by manufacturer 1 vs patients who were undergoing dialysis with e-beam dialyzers by manufacturer 2).

Logistic regression modeling was used to identify patient, treatment, and dialyzer-type characteristics associated with significant thrombocytopenia (ie, defined as a decrease in the platelet count of ≥15% and absolute platelet count of $<100 \times 10^3/\mu L$). No variable selection procedure was used to adjust for potential confounders irrespective of their statistical significance. Interactions between all statistically significant parameters were tested using Wald statistics. The log likelihood values of models with and without interaction terms were compared using the likelihood ratio test (–2 log L).

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Because the data for comparison of significant thrombocytopenia before and after change to non–e-beam sterilized dialyzers (month −1 vs month +1) included patients who had platelet counts both before and after the change in type of dialyzer, as well as patients who had measurement only before or only after the change in type of dialyzer, the data for matched pairs were analyzed using the McNemar exact test. Data for independent samples were analyzed using Fisher exact test. The repeated measurement data related to significant thrombocytopenia before and after change to non–e-beam sterilized dialyzers were analyzed using the generalized estimating equation modeling for correlated binary data. $P<.05$ from 2-sided tests was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Historical Platelet Count Data

Analysis of predialysis platelet count measurements from British Columbia dialysis units between April 2009 and February 2010 revealed that lower platelet counts were more prevalent after the switch to the polysulfone e-beam dialyzer in September 2009 (eFigure 3).

Predialysis and Postdialysis Platelet Count Measurements

Province-wide testing of all patients from British Columbia with hemodialysis in community and hospital-based facilities permitted collation of data from the majority (80%) of patients with hemodialysis from British Columbia (1706 of 2146 patients) and from Alberta (425 patients). There were no significant differences in patient characteristics of those with or without data available at this time point. Of the 1706 patients from British Columbia, 1411 patients (83%) were undergoing dialysis using e-beam sterilized membranes, 251 were undergoing dialysis using non–e-beam sterilized membranes, and in 44 patients the dialyzer type was unidentified. All 1706 patients were included in the final analysis.

In British Columbia, 11.4% of patients (95% CI, 9.9%-12.9%; n=194) had postdialysis platelet counts of less than $100\times10^3/\mu L$, 23.4% of patients (95% CI, 21.5%-25.5%; n=400) had more than 15% decrease in platelet count postdialysis, and 7.2% of patients (95% CI, 6.0%-8.6%; n=123) met both criteria. Similar proportions from the Alberta population who were undergoing dialysis using a polysulfone e-beam sterilized dialyzer made by a different manufacturer were demonstrated (10.8%; 95% CI, 8.1%-14.3%; n=46 had postdialysis platelet counts of less than $100\times10^3/\mu L$; 32.0%; 95% CI, 27.6%-36.7%; n=156 had more than 15% decrease in platelet count postdialysis; and 7.3%; 95% CI, 5.1%-10.3%; n=31 met both criteria).

Table 2 shows the comparison of patients dialyzed with e-beam dialyzers in British Columbia and Alberta with patients dialyzed with non–e-beam dialyzers in British Columbia 1 month before the switch to non–e-beam dialyzers. Patients using polysulfone e-beam sterilized dialyzers were older, had lower predialysis platelet counts and lower postdialysis platelet counts, and larger percentage decrease in platelet count. The percentages of patients with low postdialysis platelet count, significant decrease in platelet count, or who met both of these criteria were higher among patients with e-beam dialyzers compared with patients with non–e-beam dialyzers. There were no statistically sig-

Table 2. Patient Characteristics and Platelet Count Measurements Before Intervention in Patients With Hemodialysis in British Columbia and Alberta[a]

	British Columbia			Alberta	
Characteristics	Non–E-Beam Dialyzer (n = 251)	E-Beam Dialyzer (n = 1411)	*P* Value[b]	E-Beam Dialyzer (n = 423)	*P* Value[c]
Age, mean (SD), y	64.8 (15.0)	67.0 (14.8)	.03	62.3 (12.5)	.03
Male sex	150 (59.8)	840 (59.5)	.95	255 (60.3)	.96
Diabetes	137 (54.6)	703 (49.8)	.16	213 (50.4)	.33
Autoimmune disease	17 (6.8)	52 (3.7)	.02	21 (5.0)	.42
Community (vs in center) dialysis unit	85 (33.9)	526 (37.3)	.30	297 (70.2)	<.001
Platelet count, mean (SD), $\times10^3/\mu L$					
Predialysis	208 (78)	191 (80)	.004	192 (69)	.02
Postdialysis	206 (79)	179 (77)	<.001	178 (69)	<.001
Postdialysis platelet count, $\times10^3/\mu L$					
≥150	197 (78.5)	843 (59.7)		278 (65.7)	
100-149	35 (13.9)	397 (28.1)	<.001	100 (23.6)	.002
<100	19 (7.6)	171 (12.1)		45 (10.6)	
Predialysis and postdialysis Δ in platelet count, %					
Mean (SD)	0 (14)	−7 (19)	<.001	−8 (17)	<.001
<15 decrease or stable	225 (89.6)	1044 (74.0)		304 (71.9)	
15-24 decrease	15 (6.0)	233 (16.5)	<.001	66 (15.6)	<.001
≥25 decrease	11 (4.4)	134 (9.5)		53 (12.5)	
Postdialysis platelet count <100 × $10^3/\mu L$ and >15% decrease in platelet count	8 (3.2)	112 (7.9)	.007	30 (7.1)	.04

Abbreviation: e-beam, electron beam.

[a] Data are presented as No. (%) unless otherwise indicated. Before intervention indicates before switch to non–e-beam dialyzers (month −1).

[b] The e-beam sterilized dialyzers used in British Columbia and Alberta were supplied by different manufacturers. *P* values for comparison of patients dialyzed with e-beam dialyzers vs patients dialyzed with non–e-beam dialyzers.

[c] *P* values for comparison of patients dialyzed with e-beam dialyzers (manufacturer 2) vs patients dialyzed with non–e-beam dialyzers. *P* values for 3-group comparison of patients dialyzed with e-beam dialyzers (manufacturer 1), with e-beam dialyzers (manufacturer 2), and with non–e-beam dialyzers (age [$F=18.03$, $P<.001$]; male [$\chi^2=0.08$, $P=.96$]; diabetes [$\chi^2=1.93$, $P=.38$]; autoimmune disease [$\chi^2=5.46$, $P=.07$]; community dialysis unit [$\chi^2=154.47$, $P<.001$]; predialysis platelet count [$F=5.12$, $P=.006$]; postdialysis platelet count [$F=13.67$, $P<.001$]; postdialysis platelet count categorical [$\chi^2=34.02$, $P=.002$]; predialysis and postdialysis percentage change in platelet count [$F=14.71$, $P<.001$]; predialysis and postdialysis percentage change in platelet count categorical [$\chi^2=34.64$, $P<.001$]; postdialysis platelet count <100 × $10^3/\mu L$ and >15% decrease in platelet count [$\chi^2=7.22$, $P=.03$]).

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nificant differences in demographic characteristics of patients using polysulfone e-beam sterilized dialyzers and those using other types of non–e-beam sterilized dialyzers.

Factors Associated With Significant Thrombocytopenia

Analysis of patient and dialysis-related variables identified factors associated with significant thrombocytopenia (TABLE 3). Older age, primary kidney disease, lower predialysis platelet counts, and WBC counts were associated with significant thrombocytopenia. There was a significant association between thrombocytopenia and type of dialyzer used in month –1, before the switch to non–e-beam sterilized dialyzers. This was more evident in patients with previous (month –9) exposure to non–e-beam sterilized dialyzers. The combination of material (polysulfone) and sterilization process (e-beam) was statistically significantly associated with postdialysis thrombocytopenia.

In logistic regression analysis adjusting for patient and dialysis history characteristics, use of a polysulfone e-beam dialyzer was associated with an increased risk of thrombocytopenia (TABLE 4). Other factors associated with statistically significant risk of thrombocytopenia were older age and use of polysulfone non–e-beam sterilized dialyzers before the switch to the predominantly e-beam dialyzers (month –9). There were no statistically significant interaction terms.

Table 3. Comparison of Patients With and Without Significant Thrombocytopenia Before Switch to Non–E-Beam Dialyzers in British Columbia Cohort (Month –1)[a]

Characteristics	Without Thrombocytopenia (n = 1583)	With Thrombocytopenia (n = 123)	*P* Value
Age, mean (SD), y	66.3 (14.8)	70.3 (14.2)	.004
Male sex	940 (59.4)	78 (63.4)	.38
Diabetes	801 (50.6)	59 (48.0)	.57
Primary kidney disease			
Congenital	21 (1.3)	1 (0.8)	.02
Diabetes	443 (28.0)	27 (22.0)	
Glomerulonephritis/autoimmune	210 (13.3)	14 (11.4)	
Polycystic kidney disease	55 (3.5)	4 (3.3)	
Renal vascular	196 (12.4)	9 (7.3)	
Other	307 (19.4)	23 (18.7)	
Unknown	351 (22.2)	45 (36.6)	
Time receiving dialysis, median (IQR), mo	31 (13-59)	37 (13-58)	.40
Platelet count, mean (SD), $\times 10^3/\mu L$			
Δ (postdialysis – predialysis)	–8 (28)	–41 (33)	<.001
Predialysis	200 (77)	109 (38)	<.001
Predialysis $<100 \times 10^3/\mu L$	68 (4.3)	42 (34.2)	<.001
Postdialysis	191 (78)	68 (22)	<.001
% Δ (postdialysis – predialysis/predialysis)	–3 (17)	–36 (17)	<.001
White blood cell count, mean (SD), cells/μL			
Δ in postdialysis	510 (1430)	280 (1165)	.17
Predialysis	7708 (3476)	6175 (2200)	<.001
Postdialysis	7202 (3447)	5897 (2866)	<.001
Dialyzer type before switch to predominantly e-beam sterilized dialyzers (month –9)			
Polysulfone, e-beam sterilized	609 (38.5)	33 (26.8)	.004
Polysulfone, non–e-beam sterilized	432 (27.3)	51 (41.5)	
Nonpolysulfone, non–e-beam sterilized	219 (13.8)	13 (10.6)	
Not undergoing hemodialysis at month –9	323 (20.4)	26 (21.1)	
Dialyzer type before switch to non–e-beam dialyzers (month –1)			
Total patients with data available	1542	120	
Polysulfone, e-beam sterilized	1299 (84.2)	112 (93.3)	.007
Polysulfone, non–e-beam sterilized	41 (2.7)	4 (3.3)	
Nonpolysulfone, non–e-beam sterilized	202 (13.1)	4 (3.3)	

Abbreviations: e-beam, electron beam; IQR, interquartile range.
[a] Data are presented as No. (%) unless otherwise indicated. Signficiant thrombocytopenia indicates more than 15% decrease in platelet count and postdialysis platelet count of less than $100 \times 10^3/\mu L$.

Assessment Following Province-Wide Change to Non–E-Beam Dialyzers

Given the data presented herein and the potential risks associated with severe thrombocytopenia, use of all polysulfone e-beam sterilized dialyzers was stopped in both provinces and predialysis and postdialysis platelet counts were measured monthly for 6 months after the change to non–e-beam sterilized dialyzers. A 50% decrease in the percentage of patients with postdialysis thrombocytopenia in both populations was observed (FIGURE 3).

Overall, among 1784 patients, there were significant reductions in postdialysis thrombocytopenia following the change to use of non–e-beam sterilized dialyzers, such that 120 patients (6.7%; 95% CI, 5.6%-8.0%; $P<.001$) had platelet counts of $<100 \times 10^3/\mu L$; 167 patients (9.4%; 95% CI, 8.1%-10.8%; $P<.001$) had decreases in platelet counts of greater than 15%; and 38 patients (2.1%; 95% CI, 1.5%-2.9%; $P<.001$) met both criteria.

In British Columbia, the percentage of patients who had a postdialysis platelet count of less than $100 \times 10^3/\mu L$ and more than 15% decrease in platelet count declined from 7.2% (95% CI, 6.0%-8.6%) before intervention to 2.1% (95% CI, 1.5%-2.9%) after intervention ($P<.001$). In Alberta, the percentage of patients who had postdialysis platelet counts of less than $100 \times 10^3/\mu L$ and more than 15% decrease in platelet counts declined from 7.3% (95% CI, 5.1%-10.3%) before intervention to 1.6% (95% CI, 0.7%-3.4%) after intervention ($P<.001$).

Among the British Columbia cohort of 1399 patients who had predialysis and postdialysis platelet counts

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before and after the change to polysulfone non–e-beam sterilized dialyzers, 87 patients (6%) had significant thrombocytopenia before this change, 14 (1%) had significant thrombocytopenia after this change, and 13 (1%) had significant thrombocytopenia both before and after the change in type of dialyzers (McNemar test, $P<.001$). Of 307 patients who had predialysis and postdialysis platelet counts only before change to polysulfone non–e-beam sterilized dialyzers, 23 patients (7.5%) had significant thrombocytopenia vs 11 (2.9%) with thrombocytopenia among 383 patients who had predialysis and postdialysis platelet counts after change to polysulfone non–e-beam sterilized dialyzers (Fisher exact test, $P=.056$).

Using generalized estimating equation modeling for repeated data with binary outcome after adjusting for age ($P=.02$), the probability of significant thrombocytopenia was statistically significantly higher before the switch to non–e-beam sterilized dialyzers (predominantly e-beam dialyzers) vs after the switch (no e-beam dialyzer) (odds ratio, 3.57; 95% CI, 2.54-5.04; $P<.001$).

Follow-up Platelet Measurements

Of 123 patients who had postdialysis platelet counts of less than $100\times10^3/\mu L$ and more than 15% decrease in platelet count (patients with thrombocytopenia) before switching to non–e-beam sterilized dialyzers, 15 patients were no longer undergoing hemodialysis and 108 patients had predialysis and postdialysis platelet measurements at month +1. Of the 108 patients with predialysis and postdialysis platelet measurements after the switch to non–e-beam dialyzers, 95 patients (88%) had no evidence of postdialysis thrombocytopenia, whereas 13 patients (12%) had persistent postdialysis thrombocytopenia. During follow-up, the percentage of patients without postdialysis thrombocytopenia remained stable (of 96 patients who had measurements in month +3, 91 [94.8%] had no evidence of thrombocytopenia; of 87 patients who had measurements in month +5, 78 [89.7%] did not have significant thrombocytopenia).

Of 1583 patients without thrombocytopenia before the switching to non–e-beam sterilized dialyzers, 1299, 1277, and 1166 had follow-up platelet count measurements at month +1, month +3, and month +5, respectively. Fourteen of 1299 patients (1.1%) at month +1, 5 of 1277 patients (0.4%) at month +3, and 3 of 1166 patients (0.3%) at month +5 had postdialysis platelet counts of less than $100\times10^3/\mu L$ and more than 15% decrease in platelet count.

Predialysis and postdialysis platelet measurements were repeated in British Columbia in August/September 2010 (month +3/4) and October/November 2010 (month +5/6). The percentages of patients with postdialysis platelet counts of less than $100\times10^3/\mu L$ and more than 15% decrease in platelet counts remained low among those undergoing dialysis with non–e-beam sterilized dialyzers involving 17 of 1863 patients (0.91%; 95% CI, 0.55%-1.49%) in month +3 and 16 of 1767 patients (0.91%; 95% CI, 0.54%-1.50%) in month +5.

Table 4. Absolute Rates and Adjusted ORs for Characteristics Associated With Significant Thrombocytopenia in British Columbia Cohort[a]

Characteristics	No. of Events/ No. at Risk	Absolute Rate (95% CI)	Adjusted OR (95% CI)	*P* Value	*P* for Trend
Age, y					
<70	47/888	5.29 (3.95-7.03)	1 [Reference]		.02
70-79	40/473	8.46 (6.18-11.43)	1.65 (1.04-2.61)	.03	
≥80	36/345	10.43 (7.51-14.27)	1.99 (1.21-3.28)	.007	
Female vs male sex	45/688	6.54 (4.86-8.72)	0.83 (0.56-1.22)	.34	
Diabetes	59/860	6.86 (5.30-8.81)	0.96 (0.61-1.54)	.87	
Primary kidney disease					
Unknown	45/396	11.36 (8.49-15.01)	1 [Reference]		.41
Congenital	1/22	4.55 (0.24-24.89)	0.86 (0.11-6.90)	.89	
Diabetes	27/470	5.74 (3.89-8.35)	0.73 (0.40-1.34)	.31	
Glomerulonephritis/ autoimmune	14/224	6.25 (3.59-10.49)	0.72 (0.36-1.42)	.34	
Polycystic kidney disease	4/59	6.78 (2.19-17.27)	0.81 (0.27-2.44)	.71	
Renal vascular disease	9/205	4.39 (2.15-8.43)	0.39 (0.17-0.86)	.02	
Other	23/330	6.97 (4.57-10.42)	0.86 (0.49-1.52)	.61	
Duration of dialysis, mo					
<12	26/395	6.58 (4.43-9.62)	1 [Reference]		.32
12-24	17/312	5.45 (3.30-8.74)	1.25 (0.52-2.97)	.62	
>24	80/999	8.01 (6.44-9.91)	1.63 (0.77-3.45)	.20	
Dialyzer type before switch to predominantly e-beam sterilized dialyzers (month −9)					
Polysulfone e-beam sterilized	33/642	5.14 (3.62-7.22)	1 [Reference]		.05
Polysulfone non–e-beam sterilized	51/483	10.56 (8.03-13.73)	1.89 (1.36-3.45)	.01	
Nonpolysulfone non–e-beam sterilized	13/232	5.60 (3.14-9.61)	1.29 (0.66-2.54)	.46	
Not undergoing hemodialysis at month −9	26/349	7.45 (5.02-10.86)	2.10 (0.94-4.65)	.07	
Dialyzer type before switch to non–e-beam dialyzers (month −1)					
Polysulfone e-beam sterilized vs non–e-beam sterilized dialyzer	112/1411	7.94 (6.61-9.50)	2.52 (1.20-5.29)	.02	

Abbreviations: e-beam, electron beam; OR, odds ratio.
[a] Significant thrombocytopenia indicates more than 15% decrease in platelet count and postdialysis platelet count of less than $100\times10^3/\mu L$ (event).

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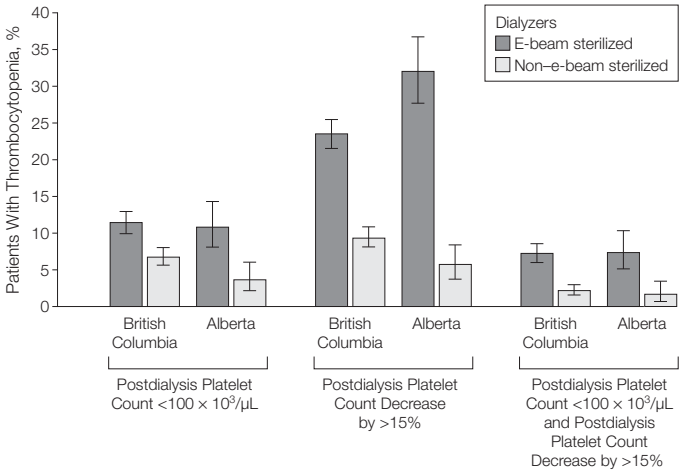
Figure 3. Significant Thrombocytopenia in Patients With Hemodialysis Before and After Change From E-Beam to Non–E-Beam Sterilized Dialyzers in British Columbia and Alberta



E-beam indicates electron beam. Error bars indicate 95% CIs. Number of patients included in predialysis and postdialysis platelet counts in British Columbia for e-beam sterilized dialyzers (before intervention), n=1706; and for non–e-beam sterilized dialyzers (postintervention), n=1784. Number of patients included in predialysis and postdialysis platelet counts in Alberta for e-beam sterilized dialyzers (before intervention), n=425; and for non–e-beam sterilized dialyzers (postintervention), n=439.

COMMENT

This systematic evaluation describes the prevalence of thrombocytopenia associated with the use of e-beam sterilized dialyzers among patients in British Columbia and Alberta undergoing hemodialysis. It demonstrates a reduction in postdialysis significant thrombocytopenia following changing to non–e-beam sterilized dialyzers, which suggests a relationship with use of the dialyzer sterilization technique.

It is biologically plausible that e-beam sterilization could induce changes in platelets by a number of possible mechanisms, but none of these have been thoroughly evaluated. Exposure to e-beam radiation may change membrane integrity, structure, or physical properties of the dialyzer and could plausibly lead to platelet activation, aggregation, or adsorption and subsequent thrombocytopenia. E-beam sterilization has become a popular method of membrane sterilization recently, because it potentially allows a more focused and precisely delivered dose of sterilization toward the dialyzer membrane.[2] Other changes may be induced through e-beam radiation at the chemical and mechanical level, such as disruption of the potting compound material that holds the individual hollow fibers of a dialyzer membrane together at both ends of the dialyzer.

Although it is generally accepted that any type of radiation sterilization does not leave residue in the dialyzer membrane, there are reports of radiation-induced alterations of dialyzer potting compound material leading to release of toxic substances that may diffuse into the patient's bloodstream during dialysis.[3] E-beam radiation of dialyzers may also produce intermediary substances that could have undesired effects on platelet activation or aggregation. However, despite the plausibility of these mechanisms, there is to our knowledge no additional evidence in the literature to support these possible theories.

Our data demonstrated that 7.2% of patients in British Columbia and 7.3% of patients in Alberta had significant postdialysis thrombocytopenia (platelet count $<100\times10^3/\mu L$ and a decrease in platelet count of >15%), and these rates exceed the normal expectations. There was also a slight decrease in WBC counts accompanying the thrombocytopenia, which could suggest a possible inflammatory effect of the process.

Repeated contact of blood with components of the dialyzer may activate the coagulation cascade and complement pathways, in addition to activating cellular components of the inflammatory cascade, including platelets.[4,5] Complement-mediated platelet activation leads to platelet aggregation and sublytic damage and could contribute to a potential decrease in platelet count early during dialysis.[6] Activated neutrophils have been shown to release a platelet activating factor exerting similar effects on platelet aggregation.[7,8]

Furthermore, dialyzer membranes may adsorb and retain platelets.[9-13] During any dialysis session, platelet counts may decline transiently but generally rebound and recover following dialysis.[14] The maximum platelet count decline observed with biocompatible membranes has been reported to be around 7% to 9%.[1] A greater decrease than this would generally be considered unusual, and thus supported our investigation of this clinical observation.

These results support the hypothesis that the thrombocytopenia observed in this dialysis cohort is due to an idiosyncratic reaction to e-beam sterilized dialyzers. All index patients experienced significant decreases in platelet count following dialysis with e-beam sterilized membranes and recovered when dialysis was performed using a non–e-beam sterilized membrane. Review of predialysis platelet counts collected during routine blood work demonstrated a steady increase in the proportion of patients with lower predialysis platelet counts since the conversion to predominantly e-beam sterilized dialyzers.

This phenomenon was observed in 2 different provinces that had changed to e-beam sterilized dialyzers made by different manufacturers. Given that the postdialysis-related thrombocytopenia occurred in 2 provinces across multiple units and geographical areas, the possibility of factors specific to a single unit, such as dialysis solutions and

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equipment supply, is much less plausible. After the discontinuation of e-beam sterilized dialyzed membranes, the number of patients with postdialysis thrombocytopenia declined. Although it would have been of academic and scientific interest to reintroduce e-beam sterilized membranes and observe for a rebound effect, we did not pursue this course because of ethical and patient safety considerations.

This association of postdialysis thrombocytopenia with the type of dialyzer used is not an isolated Canadian phenomenon; 3 case reports in 2 different US cities have reported similar findings of thrombocytopenia associated with e-beam dialyzers. In all 3 case reports, thrombocytopenia was associated with use of e-beam sterilized dialyzers and resolved when patients were switched to an alternate non–e-beam sterilized membrane.[15-17]

The occurrence of postdialysis thrombocytopenia appeared to be idiosyncratic and multifactorial. We were not able to identify other patient-specific characteristics, such as previous duration of receiving dialysis or underlying diagnoses, other than age, that were associated with postdialysis thrombocytopenia. Thus, we suspect as yet unidentified patient-specific factors may contribute to the phenomenon. Because the changes induced in the dialysis membranes after exposure to e-beam sterilization may not be uniform with regard to alterations in membrane surface integrity or potting compound material, it is possible that all dialyzers are not equally affected after e-beam sterilization. The combination of variability in patient factors, such as cytokine responsiveness and physicochemical properties of each dialyzer, may contribute to the idiosyncratic nature of the problem. Given that more cases of thrombocytopenia occurred among patients who had recently switched to e-beam sterilized dialyzers than in patients who were already undergoing dialysis with these types of dialyzers, a sensitizing event may have occurred at the time a patient was switched from one dialyzer to another.

Our study was conducted as events were unfolding. Because we were able to collect and analyze data from 2 large and distinct hemodialysis populations, we uncovered an association that might otherwise be missed or be reported only on a case-by-case basis. Furthermore, our ability to demonstrate this association in 2 provinces using dialyzers from 2 different manufacturers, but with the same e-beam sterilization technique, strengthens the observation. Further studies are needed to identify the specific mechanisms that may underlie the association between use of e-beam dialyzer sterilization and postdialysis thrombocytopenia. Given that not all patients were affected, there is a need to identify the susceptible population, perhaps based on robust biomarker and cytokine profiling.

Our study highlights 2 important points in the care of patients undergoing hemodialysis. First, dialyzer reactions such as thrombocytopenia can occur even with the use of current technologically advanced dialyzer membranes and devices. Second, these reactions may be overlooked with current routine predialysis blood work. Hemodialysis unit protocols and guidelines might consider adding postdialysis blood counts to routinely performed blood work when new dialyzers are introduced to help identify possible dialyzer-associated adverse effects.

Author Contributions: Ms Djurdjev had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kiaii, Djurdjev, Levin, MacRae.
Acquisition of data: Kiaii, Djurdjev, Jung, MacRae.
Analysis and interpretation of data: Kiaii, Djurdjev, Farah, Levin.
Drafting of the manuscript: Kiaii, Djurdjev, Farah, Levin, MacRae.
Critical revision of the manuscript for important intellectual content: Kiaii, Djurdjev, Farah, Levin, Jung, MacRae.
Statistical analysis: Djurdjev, Farah, Levin.
Administrative, technical, or material support: Kiaii, Levin, MacRae.
Study supervision: Kiaii, Levin, MacRae.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Both Drs Kiaii and MacRae reported having previously received an honorarium for giving an educational talk from Gambro. No other authors had any disclosures.
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