White Thrombus Formation in Blood Tubing Lines in a Chronic Hemodialysis Unit

Suzanne Watnick,*‡ Michael Stooksbury,* Rolf Winter,† Michael Riscoe,‡ and David M. Cohen*‡

*Division of Hospital and Specialty Medicine, and †Research and Development Service, Portland Veterans Administration Medical Center, Portland, Oregon, and ‡Division of Nephrology and Hypertension, Department of Medicine, Oregon Health and Science University, Portland, Oregon

Background and objectives: Previous reports have described white particulate matter in banked blood components, but no prior public reports describe such matter in blood tubing during the course of routine in-center hemodialysis. This report describes the events, investigations, and preliminary conclusions associated with the spontaneous formation of adherent white thrombus in the venous and arterial blood lines during routine in-center hemodialysis treatments.

Design setting, participants, & measurements: This investigation occurred at the Portland Veterans Administration Medical Center (PVAMC) Hemodialysis Unit from October 2006 through April 2007. Sixty-eight variables regarding demographics, medical history and dialysis treatments were collected on our 34 chronic hemodialysis outpatients.

Results: Over a 5-wk interval, 62% (21 of 34) of the chronic hemodialysis patients unexpectedly developed a white precipitate adhering to the luminal surface of their dialysis blood tubing, with 73 of 580 chronic dialysis treatments exhibiting the phenomenon. Microscopic and biochemical analyses were consistent with white thrombus, formed by an aggregation of platelets and fibrin. An alert was issued and other in-center hemodialysis units noted similar findings. This was remedied by the removal of specific tubing.

Conclusions: Both patient-specific and tubing-specific factors may have been operative. Although patient safety was not adversely affected, assessment of clinical and manufacturing variables potentially affecting platelet activation is warranted.


In this report, we describe the events, investigations, and preliminary conclusions associated with the recognition of white thrombus in the venous and arterial blood lines of routine in-center hemodialysis treatments. A small number of reports describe a similar phenomenon in stored blood components (1–4), but none have documented this finding during hemodialysis.

Description of Events

The PVAMC Hemodialysis Unit provides outpatient care for 34 patients (divided among four “shifts”), and provides inpatient hemodialysis on a daily basis as needs dictate. On Monday, October 23, 2006, white particulate material was noted within an outpatient’s blood tubing (Gambro Cartridge Set, Lot # 08M157304) after his hemodialysis session (Figure 1). The 1 to 3-mm particles were opaque white, homogenous, and firmly adherent to the luminal wall. The material was present in the venous lines more than the arterial lines; none was found in the drip chamber, the dialyzers (Gambro 8L, Lot # 61506H01), or the dialysate lines. The patient, assessed by a physician, reported no complaints and had no problems during or after dialysis treatment. This phenomenon was again noted at the patient’s next scheduled dialysis treatment. Another 71 observations of this phenomenon were made over the next 5 wk in 21 of 34 chronic dialysis patients.

Clinical and Administrative Response

After the second observation, variables that might be relevant to the phenomenon were collected prospectively on all 34 chronic hemodialysis patients. These variables were decided by a consensus of the chief dialysis technician, the medical director, the nurse care manager, and the manufacturer of the dialysis machine and disposables (Gambro, Inc.). The 68 variables were collected on an Excel (Microsoft Inc, Redmond, Washington) spreadsheet, and included demographic variables, medications used, medical history, type of dialysis access, and type and lot number, the tubing and lot number, type of packaging, the dialysis machine serial numbers, acid baths and bicarbonate lots, type of disinfection, shift day and time, and dialysis station. These variables also included hours of dialysis, net ultrafiltration, blood and dialysate flows, highest value for venous and arterial pressures, and which of our two reverse osmosis machines was used (#1 or #2). The group created one variable to grade the substance as ‘trace’, ‘mild’, ‘moderate’, or ‘pronounced’. At the end of the dialysis treatment, the dialysis nurse or technician examined the tubing. ‘Pronounced’ indicated white substance visible with blood still in the lines, approximately 1 mm or more in length. ‘Moderate’ was defined as white substance visible during rinseback, approximately 0.5 to 1 mm. ‘Mild’ was defined as less than 0.5 mm, and ‘trace’ was defined as particles only seen when the rinseback solution had been drained from the lines. Only one staff member observed any given line, in light of time constraints in the dialysis unit, but if a staff member was unsure of the grade, another staff member was asked to assist with grading.

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Correspondence: Dr. Suzanne Watnick, P3 NEPH, Medical Director, Dialysis Unit, PVAMC, 3710 SW US Veterans Hospital Road, Portland, OR 97239. Phone: 503-494-8490, Fax: 503-721-7810, E-mail: watnick@ohsu.edu

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Initially, the nature of these deposits was obscure. Although there was no evidence for an infectious etiology, water was assessed for bacterial counts, limulus amebocyte lysates (endotoxin), and overall composition. The permeate and feed water met standard Association for the Advancement of Medical Instrumentation quality levels (data not shown). The local water authority was contacted during this episode; no recent changes or abnormalities were noted. The dialyzer bicarbonate loop was disinfected and reverse osmosis machines were cleaned. All dialysis machines (Gambro Phoenix machines) were heat- and bleach-disinfected. Dialyzer reuse was stopped. Integrity of dialysis unit plumbing, both internal and external to the building structure, was evaluated and confirmed. The phenomenon was found to be independent of dialyzer membrane chemistry or manufacturer. Ultrapure filters were added to the dialysis circuit (as dialysate enters the dialysis machine), and new lots of heparin, darbepoetin, and erythropoietin were used. These maneuvers failed to affect the occurrence of this material.

The dialysis tubing had recently undergone packaging changes (personal communication, Gambro), so lines using old packaging methods were obtained. A variety of lots were compared and no lot-specific effects were noted. Quality control was queried at the manufacturing plant in Tijuana, Mexico; routine physical maintenance had been performed and no problems were identified by the manufacturer, as reported to us by the Gambro clinical complaints investigator. The Gambro Phoenix dialysis machine requires proprietary tubing so initially this variable could not be modified. To test tubing from a different manufacturer, all dialysis machines in our unit were replaced with rented units from a different manufacturer (Fresenius) after 73 separate observations of white clot in 62% (21 of 34) chronic patients.

On October 30, 2006, the Food and Drug Administration (FDA) and Centers for Disease Control (CDC) were voluntarily contacted. Clinical specialists from the manufacturer (Gambro) and two outside contracting agencies were consulted, including specialists in biomedical equipment and a respected national consultant for technical issues in dialysis units. Representatives from all agencies were not aware of prior similar reports. The Veterans Affairs (VA) National Center for Patient Safety was also apprised. A National VA draft advisory was prepared and distributed to all dialysis units within the Department of Veterans Affairs. Of the 13 dialysis units that used Gambro hemodialysis tubing, six responded. After this advisory, two units (33%) reported occurrences of white material in the venous blood tubing. The manufacturer questioned several non-VA-affiliated units in the Denver, Colorado area and identified a single unit where similar proteinaceous material was noted on at least one occasion.

No serious adverse events such as pulmonary embolism, myocardial infarction, cerebrovascular accident, or other thromboembolic events were noted among our chronic hemodialysis population during this period of time. Nonetheless, patients were individually informed about the unexplained nature of the occurrence, and each was offered referral to a non-VA-affiliated dialysis unit in the local community. All declined. Although there had been no evidence that patient safety was compromised, a decision was made to refer several of the patients exhibiting the most pronounced deposition to outside dialysis facilities with different equipment. The dialysis staff at the receiving units carefully monitored these patients’ blood tubing, and no repeat events were recorded. When one patient returned from such an outside unit for a single treatment, the adhesive white material was again noted at our facility. Upon conversion to the new dialysis machines and new blood tubing (Medisystems), the material disappeared; however, one of the most highly affected patients still had trace material in his blood lines for one more treatment. Other dialysis units identified by the draft advisory memo noted no further appearance of white clots after one month and observed no adverse events among patients.

The PVAMC dialysis unit attempted to return to Gambro dialysis machines along with the proprietary blood tubing. Before reinstate-ment, from March 24 to April 10, 2007, blood tubing was observed for control values. No tubing in 176 treatments had any white clot. After reinstatement of Gambro machines and blood tubing, five of 33 treatments displayed visible white clot over 2 d. We returned to use of Fresenius machines and Medisystems blood tubing, and no events were observed since that time.

Preliminary Characterization of Lumenal Material

An effort was made to establish the nature of the adherent white material. To procure material for investigation, the tubing was incised and the pliable material scraped free. Gram stain of the material was unrevealing and routine bacteriological cultures returned negative. The material remained stable in appearance when tubing sets were stored at 4°C for up to several weeks.

In preliminary chemical analysis, the material was insoluble in both PBS and in ethyl acetate; it was, however, soluble in heated concentrated potassium hydroxide, consistent with a proteinaceous nature. The material was insoluble in the ionic detergent SDS, suggesting a highly crosslinked state. Under light microscopy, the material resembled an aggregate of platelets (data not shown). Scanning electron microscopy (SEM) was performed; tubing containing deposits was incubated with saline supplemented with 2% glutaraldehyde for 24 h at room temperature, followed by extensive rinsing with distilled water. Samples of fixed blood tubing were then vacuum-dried, sputter-coated with gold (Scancoat Six, Edwards, United Kingdom), and analyzed in a scanning electron microscope (Quanta200, FEI, Netherlands), applying secondary electron emission mode in high vacuum. SEM identified platelets at varying states of activation, along with fibrin and rare embedded red blood cells (Figure 2). Pathologically, this was synonymous with so-called “white clot.” Those performing SEM did not report any abnormalities in the tubing, and stated that this tubing was not any different from similar tubing without white clot.
Assessment of Clinical Variables Potentially Associated with White Clot Formation

Baseline demographics between patients with and without clot were compared. There was no gross discrepancy between groups with respect to age, sex, race, presence of diabetes, or dialysis prescription characteristics (Table 1). We recorded a total of 73 occurrences out of 580 hemodialysis treatments performed during the 5-wk investigation period. The phenomenon was noted, to varying degrees, in 21 of 34 (62%) of our chronic hemodialysis patients. A small subset of patients exhibited pronounced deposits on multiple occasions, implying the presence of patient-specific factors; these patients experienced the same phenomenon on different machines, in different ‘stations’, and on different shifts. Interestingly, more patients initially assigned to “morning” dialysis shifts seemed to experience this phenomenon than did those on “afternoon” shifts (15 of 18 for the former versus six of 16 for the latter, \( P = 0.01 \) which was not significant after correction for multiple comparisons). When the three most affected patients were moved to afternoon shift, no improvement was noted. We compared incidence of white clot formation the prior week of morning-shift dialysis and the subsequent week of afternoon-shift dialysis and noted no difference (eight of nine morning versus seven of nine afternoon treatments exhibited clot, \( P > 0.9 \)). Dialysate calcium levels were the same between groups. Laboratory variables related to inflammation, the clotting cascade, and blood chemistries were obtained during the first week in November 2006, including platelet and white blood cell counts, blood levels of C-reactive protein, fibrinogen, hemoglobin, calcium, phosphorus, international normalized ratio and partial thromboplastin time (Table 2). All were similarly distributed among affected and unaffected patients. Hemoglobin levels were as listed below among patients exhibiting white clot compared with those without \( 12.0 \pm 1.4 \) versus \( 11.0 \pm 0.9 \) g/dl, \( P = 0.036 \), which was not significant after correction for multiple comparisons].

Aspirin (86 versus 85%) and warfarin use (10 versus 15%) was not different between groups. No other medications were over-represented among patients exhibiting white thrombus, including heparin, antibiotics, erythropoiesis-stimulating agent dose, and vitamin D analogs. Dialysis machine sterilization was not different between those with and

Table 1. Baseline demographic variables and dialysis prescription variables among chronic hemodialysis patients at the Portland VA Medical Center exhibiting (White clot) or not exhibiting (No white clot) formation of white clot in dialysis blood tubing lines

<table>
<thead>
<tr>
<th>Variable</th>
<th>White Clot ( n = 21 )</th>
<th>No White Clot ( n = 13 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD</td>
<td>65.0 ± 6.2</td>
<td>62.0 ± 5.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Male gender</td>
<td>100%</td>
<td>100%</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetic</td>
<td>9 (43%)</td>
<td>5 (38%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Caucasian</td>
<td>16 (76%)</td>
<td>11 (85%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Morning shift</td>
<td>15 (71%)</td>
<td>3 (23%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Minutes prescribed</td>
<td>179 ± 18</td>
<td>171 ± 20</td>
<td>0.24</td>
</tr>
<tr>
<td>Net ultrafiltration(^a)</td>
<td>3.1 ± 1.1</td>
<td>3.4 ± 1.2</td>
<td>0.46</td>
</tr>
<tr>
<td>Dialysis Vintage (yr)</td>
<td>4.3 ± 3.1</td>
<td>3.2 ± 2.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Blood flow rate (ml/min)</td>
<td>402 ± 34</td>
<td>394 ± 32</td>
<td>0.50</td>
</tr>
<tr>
<td>Erythropoiesis stimulating agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darbepoetin (mcg q14d)</td>
<td>54 ± 23 ( (n = 15) )</td>
<td>62 ± 32 ( (n = 10) )</td>
<td>0.40</td>
</tr>
<tr>
<td>Erthropoietin (U SQ qd)</td>
<td>8930 ± 4690 ( (n = 3) )</td>
<td>15,000 ± 7070 ( (n = 2) )</td>
<td>0.32</td>
</tr>
<tr>
<td>None</td>
<td>0 ( (n = 3) )</td>
<td>0 ( (n = 1) )</td>
<td></td>
</tr>
</tbody>
</table>

Data were obtained during the first week of November 2006 and are expressed as mean ± SD.

\(^a\)Net ultrafiltration recorded as amount at first event or first week of November 2006 if no event.
White clot in dialysis blood tubing lines

Table 2. Hematological and biochemical data for hemodialysis patients exhibiting or not exhibiting formation of white clot in dialysis blood tubing lines

<table>
<thead>
<tr>
<th>Variable</th>
<th>White Clot $n = 21$</th>
<th>No White Clot $n = 13$</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets ($\times 10^{-3}$/cm$^3$)</td>
<td>204 ± 17</td>
<td>219 ± 13</td>
<td>0.52</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>31 ± 22</td>
<td>20 ± 18</td>
<td>0.42</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>460 ± 150</td>
<td>410 ± 130</td>
<td>0.44</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.0 ± 1.4</td>
<td>11.0 ± 0.9</td>
<td>0.036</td>
</tr>
<tr>
<td>White blood cell count ($\times 10^{-3}$/cm$^3$)</td>
<td>7.0 ± 1.9</td>
<td>7.9 ± 2.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.9 ± 0.8</td>
<td>9.3 ± 0.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>4.9 ± 1.4</td>
<td>5.1 ± 1.1</td>
<td>0.63</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>1.38 ± 0.40</td>
<td>1.34 ± 0.31</td>
<td>0.76</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>33.1 ± 5.2</td>
<td>31.7 ± 4.3</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Laboratory values were obtained during the first week of November 2006, reported as value ± standard deviation.

Discussion

We describe the sudden emergence of white clot deposition in the arterial and venous blood lines during a 5-wk period in late 2006 in a hemodialysis unit in the Northwestern United States. This phenomenon has not previously been described in the public domain; however, a similar white particulate matter was described in blood products stored ex vivo in plasticized containers (1–4). This phenomenon seemed to abate after change of dialysis blood lines, and returned immediately after temporary reinstatement of prior dialysis blood lines.

Activation of the clotting cascade during hemodialysis is not unexpected. Surface interactions between artificial materials and blood cause platelet activation and adhesion (5). Air is usually present in the drip chamber, and air/blood interactions similarly promote thrombotic activity. With current manufacturing practices, however, the proprietary lumenal surface chemistry of dialysis blood tubing is engineered to minimize thrombogenicity. According to plastics experts and an independent technical dialysis advisor (personal communication, Dalibor Smejtek and Jim Curtis, Jim Curtis and Associates, LLC, Dialysis Consulting Services), this process is generally well defined and safe, but potentially prone to error. Irregularities in the plastic could entrap microbubbles, which can enhance thrombogenicity. The polyvinyl chloride itself, may cause clotting or adsorption of blood material due to calcium content, charge, or surface irregularities.

White thrombus usually forms under conditions of high flow velocities and is often manifest in arteries and arterioles. The thrombi are mainly platelet and fibrin-rich (hence the white color), due partly to rheologic properties of vessels (6,7). High (i.e. arterial) flow velocities produce high shear stress, with flow rates relatively reduced closest to the vessel wall; these conditions foster local platelet activation (8) and are present during dialysis.

The above information gives biological rationale for white thrombus formation in dialysis blood tubing. It was reported to us that another manufacturer experienced a similar phenomenon with resultant white thrombus over 20 yr ago after a possible problem with tubing manufacturing, but the report remained internal (personal communication). Representatives from Gambro, Inc. identified two other internal reports (from Australia in 2002, using non-Gambro lines, and from Yugoslavia in 2003, using Gambro lines) describing the appearance of white thrombus in tubing after SEM analysis. With time, the phenomenon disappeared. (Faxed report from Gambro Renal Products Clinical Complaint Investigator). Three other dialysis units experienced white clot formation at the time of this investigation after they were alerted to this possibility. This phenomenon may be more pervasive than is suggested by the lack of published reports.

Although the association between hemoglobin and the presence of white clot was not statistically significant after the correction for multiple comparisons, eight patients in the group that developed white clot exhibited hemoglobin levels that exceeded the highest hemoglobin level in the group that did not develop white clot. It is interesting to note that an elevated hematocrit adversely affects blood rheology and promotes clot formation (8). Given the small sample size, perhaps this should be considered for future hypothesis testing if white thrombus is found more commonly. This may be noteworthy in light of recent observations questioning the safety of targeting hemoglobins in excess of 12 g/dl in patients with advanced chronic kidney disease or dialysis-dependence (9–12).

The increased number of events in morning-shift patients was also not stochastically significant after adjustment for multiple comparisons, and our morning patients continued to experience this when dialyzed in the afternoon, as compared above. There was no difference in dialysis prescription characteristics, such as dialysis time or ultrafiltration, between morning and afternoon groups. Typically, morning-shift dialysis patients have been on dialysis longer, and may have a modified response to potential thrombogenic factors; our morning group was on dialysis an average of 1.1 yr longer than the afternoon shift, but this was not statistically significant (see Table 1).

In providing recommendations for nephrologists who may encounter this unusual complication, we propose that dialysis staff be informed of the phenomenon of white thrombus, possibly by the medical director of the dialysis unit, so it could be recognized if it occurs again. If this does occur, we propose an investigation into cause without any
immediate changes, given our experience that no serious adverse events occurred in the short term. Nothing more would need to be done if the phenomenon disappears within a month, as it did in three other units. If the phenomenon does not abate, we think it reasonable to consider a change of hemodialysis blood tubing, because this maneuver eliminated the problem at our unit, and because long-term consequences of either the presence of the particulate matter, or of conditions leading to its formation, remain unknown.

Conclusion

In this report, we describe the events and findings associated with white thrombus formation in blood tubing sets during hemodialysis. Previous public reports describe white thrombus in banked blood components, and several internal company reports record this in dialysis blood tubing similar to ours. Variables potentially affecting this phenomenon were identified in the study presented here. An element was patient-specific; the phenomenon was repeatedly observed in only a subset of dialyzed patients. A second component was contributed by the unique properties of the blood lines themselves; conversion to lines from a different manufacturer essentially prevented white clot formation, which returned with use of the former lines. We believe it is important for the nephrology community to be familiar with these events, and to be vigilant for the emergence of similar findings in other dialysis units.

Acknowledgments

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Disclosures

None.

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