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BRIEF REPORT

The incidence of thrombocytopenia associated with continuous renal replacement therapy in critically ill patients

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Abstract

Introduction: Thrombocytopenia in the intensive care unit (ICU) is a commonly experienced complication; the pathology is not always easily understood. Continuous renal replacement therapy (CRRT) provides a method to dialyze unstable critically ill patients. We hypothesized that CRRT may precipitate a form of thrombocytopenia. In trials thrombocytopenia occurred at rates as high as 70%. The etiology remains unknown and results in additional diagnostic workup, as well as possible drug therapy. The extent, duration and temporal relation of thrombocytopenia remain to be determined. *Objectives*: Identify a pattern in platelet fluctuations after the initiation of CRRT and its impact on health care. *Methods*: A retrospective study was conducted in patients receiving CRRT for >24 h with no pre-existing thrombocytopenia. Patients initiated on CRRT had daily platelet counts monitored, and CRRT attributes and therapeutic interventions were collected. Platelets were assessed for time to nadir, degree of decline and time to return to baseline after discontinuation of CRRT. *Results*: Forty-nine patients met inclusion criteria. Thirty-seven percent of patients receiving heparinoids were tested for heparin-induced thrombocytopenia (HIT), during CRRT, with 39% of these patients having therapy changed to non-heparinoid agents due to suspected HIT; no HIT antibodies were positive. Eleven patients (22%) receiving anticoagulants, prophylactically or therapeutically had them held for a drop in platelets. There was a mean decline in platelets of 48% with a mean of 4.6 days to the nadir. An average 2.48 days were observed until rebound to $>150 \times 10^3/mm^3$. Statistical analysis failed to identify any patient attributes that correlated with the probability of thrombocytopenia. *Conclusion*: CRRT appears to be associated with a drop in platelets within the first 5 days of therapy with an average decline of 48%. However, platelets appear to return to $>150 \times 10^3/mm^3$ after cessation of CRRT. This fluctuation should be considered in the setting of patients developing thrombocytopenia after initiation of CRRT.

Keywords

Continuous renal replacement, heparin-induced thrombocytopenia, renal replacement therapy, thrombocytopenia

History

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Background

Attempting to identify the cause of thrombocytopenia in critically ill patients can be convoluted. Thrombocytopenia occurs in as much as 70% of patients receiving continuous renal replacement therapy (CRRT).[1] CRRT provides a method to dialyze patients too critically ill and unstable to receive conventional hemodialysis (HD). Thrombocytopenia in HD has been documented with a number of proposed mechanisms: drug induced, auto-immune, splanchnic sequestration and dialyzer membrane issues.[2] The etiology of thrombocytopenia associated with CRRT remains unknown and frequently results in diagnostic workup, product utilization and therapeutic interventions. The extent, duration and temporal relation of thrombocytopenia still remain to be determined. This was a retrospective evaluation of platelet fluctuations seen with CRRT and its impact on therapeutic choices in the intensive care unit (ICU).

Methods

Patients admitted between February 1, 2012 and January 31, 2013 to the medical, surgical, cardiovascular and neuroscience ICUs receiving CRRT, by mode of continuous veno-venous hemofiltration or continuous veno-venous hemodiafiltration, for more than 24 h were reviewed. The institution utilizes the NxStage system one® continuous renal replacement system with NxStage® Purema polyethersulfone membrane. Exclusion criteria included thrombocytopenia prior to CRRT ($<50 \times 10^3/mm^3$), more than two unscheduled filter changes in a 24-h period, or active bleeding. Data were collected on baseline platelet counts, demographics, admission diagnosis and comorbid conditions as well as indication and duration of CRRT, flow rates and anticoagulation. Modifications to anticoagulation and investigation of thrombocytopenia, including monitoring, heparin-induced thrombocytopenia (HIT) antibodies, and changes in anticoagulation were recorded. Antiplatelet and anticoagulants

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were continued through CRRT consistent with standard of care. Data were collected on antiplatelet and anticoagulants utilized during CRRT, and reasons for discontinuation when available.

Upon initiation of CRRT, baseline platelet counts were recorded. Subsequent, daily counts were then recorded throughout therapy and 7 days following discontinuation. A change in platelets was defined as the percentage change from platelet count on the day prior to initiation and nadir experienced during CRRT. Return of counts was defined by a return of platelets to >150K or return to baseline, whichever came first. Admission diagnosis was divided into four groups including medical (infection or pulmonary), surgery (surgical issues or trauma), cardiovascular (cardiothoracic surgery) and neurological (stroke). If a HIT antibody was ordered or therapeutic intervention was initiated during CRRT or in the 7 days following, results and treatment were recorded. For the purposes of this study a drop of $\geq$50% of platelet count was considered significant.

Statistics

For descriptive summaries of baseline characteristics, the mean and standard deviation are reported for numeric variables, and the frequencies and percentages for categorical variables. Two-way associations among categorical variables were summarized using the Pearson Chi-square test (or Fisher's exact test if there are small expected frequencies). Comparisons of numeric variables between groups were made using the Wilcoxon rank sum test. Time to minimum was estimated using Kaplan–Meier product limit estimates. Comparisons of time to minimum across groups were made using the log-rank test. The association of age in years with time to minimum was made using Cox proportional hazards regression with age as a continuous variable. No adjustment was made for multiple testing in this descriptive pilot study.

Results

Forty-nine patients met inclusion criteria with a male predominance and an average age of 60 years old. Indications for CRRT were acute kidney injury (AKI) (57%), chronic kidney disease (CKD) (27%) and AKI on CKD (16%). A medical diagnosis was the most common reason for admission (30.6%), followed by a cardiovascular diagnosis (Table 1). Following initiation of CRRT, there was an observed decline in platelet counts by an average 47.8% to the nadir during therapy; the average time to nadir was roughly 5 days. Platelets recovered with average of 2.5 days after discontinuation of CRRT. Six patients (12%) had recovery of platelets while receiving CRRT. Most patients

Table 1. Patient demographics.

	Total ($N=49$)	<50% reduction in platelets ($n=24$)	>50% reduction in platelets ($n=25$)
Patient demographics			
Male (%)	55	75	36
Age (yrs)	60 (±14.7)	61	59
Baseline platelets ($\times 10^3/mm^3$)	227 (±117)	241	205
Platelets on day 1 of CRRT ($\times 10^3/mm^3$)	176 (±101)	184	167
Comorbid conditions (%)			
Hepatitis	8	4	12
Diabetes	53	67	40
Hyperlipidemia	20	21	20
Chronic kidney disease	35	29	40
Peripheral artery disease	29	46	12
Hypertension	73	71	76
Cancer	8	12	4
Heart failure	35	33	36
Atrial fibrillation	14	12	16
Hypothyroidism	14	12	16
COPD	10	4	16
Admission diagnosis (%)			
Infection/respiratory	26	12	14
Cardiovascular	12	6	6
Trauma/surgery	5	3	2
Neurological	6	3	3
Therapy characteristics			
Dialysate flow rate* (L/h)	2.75 (±0.72)	3	3
CRRT blood flow rate (mL/min)	325 (±34.2)	331	308
CRRT duration (days)	6.33 (±5)	6	6.56
Unscheduled filter changes	0.86 (±1.11)	1	0.56
Indications for CRRT (%)			
AKI	57	58	56
CKD	27	25	28
AKI on CKD	16	17	16
Anticoagulant (%)			
None	14	17	12
Subcutaneous heparin/LMWH	61	63	60
Heparin infusion	25	21	28
Sodium citrate	12	12	12

*Includes both dialysate and replacement fluids given inclusion of both CVVHD and CVVHDF modalities.

received deep vein thrombosis (DVT) prophylaxis with subcutaneous heparin or enoxaparin (61%) with 25% of patients receiving therapeutic anticoagulation. Thirty-seven percent of patients receiving heparinoids were tested for HIT during CRRT, with 39% of these patients having therapy changed to non-heparinoid agents due to suspected HIT; of which no HIT antibodies were positive. Heparin therapy was resumed in all patients as soon as deemed clinically safe to resume after negative HIT. Eleven of the patients receiving anticoagulants (22%) had prophylaxis held due to a precipitous drop in platelets. Seven patients (14%) had anticoagulants held due to complications of bleeding, however bleeding did not appear to occur any more frequently when platelets dropped >50% (Table 2).

Fifty-one percent of patients met criteria with a significant drop in platelets. When evaluating predictors of a significant reduction in counts, female sex was the only attributable factor found to be correlated ($p < 0.009$). No other attributes appeared to be associated with a significant decline in platelets (Table 2). A trend towards a longer time to nadir in women (4 vs. 6 days, $p = 0.17$) was seen, however this did not reach statistical significance. Time to nadir was not altered by indication for CRRT ($p = 0.71$) or admission diagnosis ($p = 0.76$). This may signify that female patients may have a sustained effect of CRRT on platelets resulting in an overall larger reduction in platelet counts.

Discussion

This research suggests an association between CRRT and a decline in platelet counts. We documented an average decline of 47.8% occurring at a mean of 5 days after the initiation of CRRT. This decline appeared to be transient as platelet counts did rebounded 2.5 days after cessation of the treatment. The absolute cause of this decline has not been identified, but could be consumptive in nature, as similar to that seen in other extracorporeal therapies.[2,3] The decline in platelets frequently led to alterations of therapy and/or diagnostic workup requiring treatment, which may not be indicated otherwise. Eighteen patients (37%) where evaluated for HIT with seven patients deviating from standard of care. While the average decline in patients evaluated for HIT was 55%, as consistent with recommendations for the evaluation of HIT, diagnosis is contingent on the absence of

Table 2. Impact on therapy and patient characteristics associated with platelet decline.

Platelet statistics			
Mean platelet count at CRRT initiation ($\times 10^3/mm^3$)	176.5 (±101)		
Mean platelet change (%)	47.8 (± 25.1)		
Mean minimum platelet count ($\times 10^3/mm^3$)	91.7 (± 75.4)		
Time to minimum (days)	5.4 (± 3.7)		
HIT antibody	18		
Mean drop in platelets (%)	55		
HIT therapy initiated	7		
Mean drop in platelets (%)	66		
Therapeutic interventions	<50% reduction in platelets ($n = 24$)	>50% reduction in platelets ($n = 5$)	
HIT antibody	6	12	
Positive result	0	0	
Heparin therapy held	7	11	
Due to bleeding	4	3	
Due to platelet count	3	8	
HIT therapy initiated	1	6	
Factors associated with thrombocytopenia	<50% reduction in platelets ($n = 24$)	>50% reduction in platelets ($n = 25$)	*p* Value
Sex			0.0096
Male	18	9	
Female	6	16	
CRRT Indication			1
AKI	14	14	
CKD	6	7	
AKI on CKD	4	4	
Admission diagnosis			0.9696
Infection/respiratory	12	14	
Cardiovascular	6	6	
Trauma/Surgery	3	2	
Neurological	3	3	
Circuit anticoagulation (systemic heparin or circuit citrate)			0.8446
Yes	8	9	
No	16	16	
Questionable disseminated intravascular coagulopathy*			0.675
Yes	6	5	
No	18	20	

*Questionable DIC defined as patients with a significant decline in conjunction with a progressively widening of coagulation parameters.

other causes of thrombocytopenia.[4] These alterations have the potential to pose threat to patients and impact health care costs by unnecessary diagnostic and therapeutic interventions. To highlight the impact this may have on cost, standard of care with subcutaneous heparin or heparin infusion costs in our institution is roughly $4.50/day and $19.00/day for an average 70 kg patient. These costs are similar in the event enoxaparin is utilized, costing $6.00/day and $23.00/day for prophylactic and treatment doses, respectively. When comparing the therapeutic alternative for patients with HIT, argatroban, costs would equal $1430.00/day, a substantial difference. Clinical workup must also be taken into consideration with the addition of a HIT antibody at our institution averaging $170.00/test. While these costs are specific to the institution in which this research was completed, the difference in cost is obvious. Further research is needed to determine patient populations most at risk, the pathology and the potential methods to differentiate this thrombocytopenia due to CRRT from other processes.

A significant decline of platelets in these patients can signify potentially serious complications, such as HIT. HIT remains as one of the feared sequelae associated with the use of heparin. A precipitous fall in platelets frequently triggers the need to investigate further in patients receiving heparin. However, a similar drop in platelets may be seen in CRRT and without documentation of platelet patterns associated with CRRT this commonly necessitates testing to rule out HIT. Techniques for the diagnosis of HIT in patients on CRRT still remain to be identified. Documentation of normal platelet trends in CRRT patients may provide a basis for avoiding inappropriate testing and/or treating HIT.[1] Platelet declines have been documented in CRRT, Schilder et al. identified a rate of thrombocytopenia in 25% of patients. These researchers deemed this drop as clinically suspected HIT despite never being confirmed by further laboratory evaluation.[5] Literature assessing the use of citrate, a regional anticoagulant, versus the systemic anticoagulant heparin has eluded to thrombocytopenia in CRRT. In a comparison of citrate versus heparin circuit anticoagulation, there was a significantly lower rate (3% vs. 10%) of thrombocytopenia, defined in these studies as HIT.[6,7] However, the authors provide no explanation of the cause of ''HIT'' in the citrate group. While these patients received heparin in line with standard of care, the rates of HIT in these trials were substantially higher than that commonly seen, 0.5–2.5%, respectively. This higher incidence indicates either a substantially elevated risk of developing HIT, a concept not supported by the lack of positive testing identified in the current study, or an alternative cause of thrombocytopenia in this population.[8,9] This potentially indicates that there is a process other than immune-mediated HIT resulting in a decline in platelet counts.[6,7] The use of circuit anticoagulation, a factor which has been historically associated with reduced rates of thrombocytopenia, could have contributed to a decreased occurrence in these trials.[10] In one retrospective analysis, a similar platelet decline around 35% was seen between days 1 and 7 in patients placed on CRRT for HIT.[1]

The cause of the thrombocytopenia in patients on CRRT remains to be determined. Given the frequent occurrence of thrombocytopenia in the critically ill patient population there are a number of potential etiologies including the severity of illness of patients requiring CRRT, the number of administered medications and comorbid conditions. The loss of platelets through the hemofilter or consumption through the system may also occur. Thrombocytopenia in patients receiving both heparin and non-heparin anticoagulation for CRRT make the likelihood of heparin-induced immune-mediated thrombocytopenia less likely. The higher occurrence of thrombocytopenia in the heparin groups may be second to its inferiority at maintaining circuit patency resulting in an increase in filter changes.[7,11] Given exclusion of patients with more than two unscheduled filter changes, this suggests an etiology of thrombocytopenia other than loss through clotted hemofilters. This may signify that the drop in platelets may have minimal to no association with blood volume lost in unscheduled filter changes. Mulder et al. suggested that the hemofilter itself may contribute to the platelet loss seen during CRRT by means of destruction or retention; they further suggested that the loss may be attenuated by higher blood flow rates. In a paired data set of 48 patients, the mean platelet count dropped 2.3×10^9 per liter of flow. This platelet loss was strongly related to blood flow rate with a decrease in loss of platelets for every mL/min increase in blood flow. The authors estimated a total daily platelet loss of 625×10^9 cells, displaying the demand placed on platelet production to maintain counts.[12] The filter type has also been implicated in platelet loss, suggesting a more substantial decline depending on hemofilter type. Liu et al. compared platelet loss across a polysulfone and cellulose triacetate filters with or without anticoagulation. Patients with cellulose triacetate filters and those with CRRT circuit anticoagulation had significantly lower occurrence of thrombocytopenia.[10] These authors also identified a lower rate of platelet activation with the triacetate filter by monitoring the level of bound GP IIb/IIIa. While the literature is minimal, this data signifies not only the presence of a reduction in platelets in patients on CRRT, but the relation of specific CRRT attributes to the risk and degree of platelet loss.[1,10,12] Missing from this literature is the pathology in which thrombocytopenia develops. Oever et al. suggested a trapping phenomenon in the extracorporeal circuit resulting in activation of the platelets and sequestration. A portion of patients in this study even expressed PF4 antigens after activation, posing the possibility for an immune mediate response similar to that seen in HIT, but not identified with HIT antibody assays.[13]

This research further substantiates the minimal amount of literature evaluating the effects of CRRT on platelets in critically ill patients. It appears that there may be an association between female gender and the risk of thrombocytopenia. Unlike past data there was no correlation identified between circuit anticoagulation or circuit flow rate and the rate of thrombocytopenia.[10,12] We did however evaluate the impact of this platelet decline on the care of patients. Patients experiencing a decline in platelets had a substantially greater rate of being tested and treated for HIT, as well as holding anticoagulation. Future research should look to identify etiologies of thrombocytopenia during CRRT, methods to identify when thrombocytopenia is secondary to CRRT and methods to avoid profound thrombocytopenia.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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