CKJ

Original Article

Inpatient hemodialysis without anticoagulation in adults

Sheena Sahota and Roger Rodby

Division of Nephrology, Rush University Medical Center (RUMC), Chicago, IL, USA

Correspondence and offprint requests to: Roger Rodby; E-mail: rogerrodby@mac.com

Abstract

Background. Anticoagulation use during hemodialysis (HD) is standard practice but issues related to an increased risk of hemorrhage associated with inpatients make this a concern.

Methods. An anticoagulation-free protocol in which (i) the dialysis circuit is aggressively primed with normal saline (NS) in an attempt to flush it of all air, (ii) blood flow during the HD treatment is maximized to up to 400 mL/min, (iii) the dialysis circuit is flushed every 15 min with 100 mL of NS, and (iv) the use of bloodlines that lack a blood–air interface was developed and used for all adult inpatient HD treatments at Rush University Medical Center. The purpose of this study was to evaluate the rate of HD circuit clotting using this approach and to determine if factors such as access type, blood flow, arterial and venous bloodline pressures, the need for reversing the arterial and venous access lines for low blood flow or high venous or arterial bloodline pressures, or the amount of net ultrafiltration were associated with HD circuit clotting. Patients were excluded from analysis if they were on a heparin drip, clopidogrel, warfarin or direct thrombin inhibitors. We reviewed 400 HD treatments in 400 adult patients from 12/12 to 10/13.

Results. The HD access in these patients consisted of catheters in 45%, native AV fistulas in 40% and grafts in 15% of the patients. The average blood flow in the treatments was 378 ± 46 mL/min. In 5% of the treatments, the arterial and venous bloodlines were reversed. Only 4 of the 400 (1%) of the treatments clotted the dialysis circuit. Factors associated with clotting were lower achieved blood flows (225 ± 50 mL/min versus 379 ± 44 mL/min), higher arterial bloodline pressures (-198 ± 24 mmHg versus -151 ± 45 mmHg) and reversal of arterial and venous access lines.

Conclusion. Our anticoagulation-free protocol allows inpatient HD to be performed in adults across all access types and with essentially no circuit clotting.

Keywords: anticoagulation; hemodialysis; heparin

Introduction

Because hemodialysis (HD) requires extracorporeal blood flow, heparin use during treatment is standard practice in both the out- and inpatient settings [1, 2]. While this is not generally problematic for stable outpatients receiving HD, many issues associated with the inpatient make the use of anticoagulation during HD a concern. Alternative strategies include heparin-coated dialysis membranes and the use of a citrate-based dialysate [1, 2]. While these maneuvers were developed to reduce or eliminate the need for systemic heparin administration during HD, heparin was still required in the majority of the studies, and in those that eliminated it altogether, HD circuit clotting was not uncommon [3–9]. In 2000, we developed an anticoagulation-free HD protocol based on aggressive intradialytic normal saline (NS) flushing of the dialyzer, for the inpatient HD treatments at Rush University Medical Center (RUMC), Chicago, IL, in which anticoagulation was of specific concern. Since 2008, all inpatient treatments utilized this protocol in which no heparin or other forms of anticoagulation were used. To determine the effectiveness of this 'blanket' approach, we determined the incidence of and factors associated with HD circuit clotting utilizing our anticoagulation-free HD protocol.

Methods

A retrospective chart review was done on all adult (>18 years) RUMC inpatient HD treatments, both end-stage renal disease (ESRD) and acute kidney injury (AKI) from December 2012 to October 2013. Patients were excluded from analysis if they were on heparin, clopidogrel, warfarin or direct thrombin inhibitors. Patients on aspirin were included in the analysis. We identified 400 unique patients (patients were not used for more than one hospitalization) and evaluated the first HD treatment of their hospitalization. The patient demographics (including age, race, gender, height, weight and BMI) and comorbid conditions (diabetes mellitus and hypertension) were recorded. Their medications prior to admission and through their first HD treatment, as well the patient's access, the specifics of the dialysate, the dialyzer type and blood tubing were

collected. The blood urea nitrogen, creatinine, albumin, protime/international normalized ratio, partial thromboplastin time and platelet counts prior to the first HD session were documented. For each HD treatment, the average blood flow rate and the average arterial and venous pressures were calculated. In addition, the amount of net ultrafiltration (excluding the flushes) for each treatment was recorded. We also determined if a treatment required the reversal of the arterial and venous blood flow lines of the access in the setting of high venous or arterial bloodline resistance pressures. Clotting of the circuit was defined by complete clotting requiring replacement of the blood tubing and dialyzer to complete the treatment. We determined which treatments had clotting of the dialysis circuit and whether or not this was associated with access type, reversal of bloodlines, dialysis treatment blood flow, venous or arterial pressures of the dialysis circuit and the net ultrafiltrate (UF).

All HD treatments were performed using Fresenius® K dialysis machines with F160NR polysulfone dialyzers and Medisystems® Streamline airless system set bloodlines. Blood flow was ordered at 400 mL/min and only decreased if the access could not support that number. Dialysate did not contain citrate. After each HD session, dialysis catheters were locked with 5000 units/mL of heparin to fill the dead space of each of the venous and arterial sides, the amount depending on the brand of double lumen catheter. Prior to each treatment, the heparin was removed by extracting 3–5 mL of blood from each catheter port, which was discarded and a separate syringe filled with NS flushed both ports of the catheter.

The anticoagulation-free protocol consisted of

(i) Priming the hemodialyzer with 0.9% NS at a pump speed (PS) of 200 mL/min.
(ii) Recirculating the NS at PS 500 mL/min for 30 s or until all air has been removed from the bloodlines and hemodialyzer.
(iii) Continued recirculation of the NS at PS 200 mL/min for 10 min.
(iv) During the HD treatment, the hemodialyzer is flushed every 15 min with 100 mL of 0.9% NS. This is achieved by clamping off the bloodline and opening up a preattached bag of NS to the blood pump until 100 mL had been flushed through the dialyzer. This is done using the same pump rate that is used for the blood during treatment, and thus the NS flush takes ~15–20 s. The total volume amount of NS flushes anticipated during a treatment is precalculated into the total ultrafiltration fluid removed during the HD treatment.
(v) Unless contraindicated, blood flows of 400 mL/min are a standard order.
(vi) Use of 'airless' bloodlines.

Comparisons between treatments that clotted and those that did not were done using unpaired t-tests and Fisher's exact test.

Results

Table 1 shows the baseline patient characteristics for the 400 treatments of the 400 qualifying patients (adults requiring HD but not previously on or requiring anticoagulation before their first inpatient HD treatment). The majority of the patients had ESRD and represented the typical outpatient with ESRD in the USA on HD: middle aged, African American with diabetes and hypertension. The

Table 1. Baseline patient characteristics

ESRD/AKI	84/16%
Age (mean ± SD)	56.3 ± 15.1
BMI (mean ± SD)	28.4 ± 8.1
Male (%)	52
African American (%)	64.5
Diabetes (%)	46.8
Hypertension (%)	89.7
History of peripheral blood clot (%)	10.5
ASA (%)	45.8
BUN (mmol/L) (mean ± SD)	20 ± 11 (57 ± 31 mg/dL)
Albumin (g/L) (mean ± SD)	31.4 ± 0.68 (3.1 gm/dL)
Platelet count (thousand/μL) (mean ± SD)	185 ± 87.3
INR (mean ± SD)	1.2 ± 0.2
Access: catheters/fistulas/grafts	45%/40%/15%

access type reflected what may represent sicker or more chronically ill patients with the highest percentage receiving dialysis through a venous catheter (45%) and only 40% were dialyzed through a native fistula.

The average blood flow of all HD treatments was 378 ± 46 mL/min with AV fistulas 390 ± 30 mL/min, AV grafts 383 ± 38 mL/min and HD catheters 365 ± 56 mL/min. Reversal of arterial and venous bloodlines for low blood flow or increased venous pressure was required in 21 treatments (5.3%).

Only 4 (1%) of the 400 HD treatments were associated with clotting of the hemodialyzer circuit. None of the baseline patient characteristics from Table 1 was associated with clotting. Three of the four clotted treatments were seen when the bloodlines were reversed (P < 0.01). Other factors associated with clotting were (i) the arterial pressures: −198 ± −24 in treatments that clotted versus −151 ± −45 in those that did not (P = 0.04) and (ii) the blood flow: 225 ± 50 mL/min in treatments that clotted versus 379 ± 44 mL/min in those that did not (P < 0.01). Factors not associated with clotting were (i) the venous pressures: 128 ± 61 in treatments that clotted versus 140 ± 45 in those that did not (P = 0.70) and (ii) the net UF amount (not including flushes): 1000 ± 817 mL/HD in treatments that clotted versus 2017 ± 1366 in those that did not (P = 0.14). Although three of the four clotted treatments were inpatients with a catheter, this trended towards but was not a statistically significant finding (P = 0.2).

Discussion

Our anticoagulation-free NS flush HD protocol allows inpatient dialysis treatments to be done successfully without the need for anticoagulation and with minimal circuit clotting. Since inpatients often have a number of comorbid conditions related to their admission or that may develop during their admission that puts them at risk of increased morbidity and mortality if bleeding occurs from dialysis-related anticoagulation, the ability to avoid such a risk is certainly welcomed.

HD, from its start, has required anticoagulation to prevent circuit clotting. ESRD patients are already at an increased risk of bleeding for reasons including a higher incidence of gastrointestinal arteriovenous malformations; azotemia-associated platelet dysfunction and altered platelet vessel wall interactions [1, 10]. The risk of bleeding increases even further in the inpatient setting because of surgeries, intracranial events, immobilization requiring prophylactic anticoagulation and the increasing use of antiplatelet or other antithrombotic medications often used in the setting of cardiac events [11].

Many forms of anticoagulation have been used during dialysis, but unfractionated heparin is most commonly used because of its low cost and availability [1, 2, 10]. In addition to increasing the risk of hemorrhage, heparin can also cause hypertriglyceridemia by reducing endothelium-bound lipoprotein lipase, contribute to hyperkalemia by suppressing aldosterone production in the zona glomerulosa and is associated with immune and non-immune mechanisms that can lead to mild-to-severe thrombocytopenia and with or without thrombosis [1].

Several strategies have been utilized on inpatients in an attempt to avoid the risks of anticoagulation seen with typical heparin use in HD, predominantly hemorrhage. Two 'regional' anticoagulation protocols have been developed. The first utilized heparin at the front end (pre-filter) and protamine post-filter while the other protocol used citrate with calcium in a similar set-up [1, 2, 10, 11]. Protamine binds heparin and makes it inactive. Regional anticoagulation with heparin and protamine was burdensome, often required coagulation status monitoring using the activated clotting time during the procedure with a point of care measurement device. Even with monitoring, frequent extracorporeal clotting and rebound bleeding several hours after the procedure were not uncommon as the half-life of heparin does not match that of protamine, and protamine itself has anticoagulant properties [12]. Regional anticoagulation with citrate and calcium has been shown to be more precise and is associated with a decreased risk of bleeding compared with dialysis using heparin alone [13]. Citrate binds plasma calcium thereby preventing progression of the coagulation cascade; however, electrolyte abnormalities could occur including hypocalcemia if insufficient calcium is replaced on the blood return side of the circuit, hypercalcemia if excessive calcium is administered; hypernatremia from tri-NaCitrate; and metabolic alkalosis through the metabolism of citrate [13]. Lower dose heparin regimens have also been developed in which the amount of heparin is minimized. Even with this approach in one study, 10% of the patients considered at risk of hemorrhage developed a bleeding complication, which rose to 38% inpatients considered at 'high risk' for bleeding [14]. The use of an infusion of prostacyclin (a platelet aggregation inhibitor) during HD as a heparin-sparing approach was reasoned to be a better method for high-risk HD patients because of its short half-life. However, due to multiple side effects such as hypotension, chest pain, headache and flushing, this strategy lost favor [12].

Dialysate concentrate that is acidified with citric acid instead of less physiologic acetic acid has been developed to improve hemodynamics as well as the acid-base status of patients receiving HD. This 'citrate-enriched' dialysate also has the advantage of small concentrations of citrate diffusing into the blood with a subsequent effect of mild circuit anticoagulation. And while the amount of citrate in the blood of the circuit is considerably less than that seen with classic regional citrate anticoagulation, it nevertheless provides an opportunity to limit heparin usage. Despite this, one study using citrate-containing dialysate found no difference in heparin usage [8] while another study attempted heparin-free treatments, however complete circuit clotting occurred in 22% of the treatments [9].

Another maneuver to minimize or avoid heparin has been the coating of dialysis membranes with heparin. Many of these studies report significant reductions in systemic heparin requirements, but are not heparin free [3, 4, 7]. Others have attempted to use heparin-coated membranes

to eliminate the need for any systemic heparin. Mujais developed a protocol meant to avoid systemic heparin altogether during HD by priming a Hemophan (Gambro, Lakewood, CO) dialyzer, which has a high affinity for binding heparin, with 12–20 0000 units of heparin in a liter of NS that was recirculated for 30 min before the HD treatment started. Twelve patients underwent three treatments (total 36 treatments). Clotting of the circuit requiring replacement occurred in three treatments (8%) [6]. The results of the HepZero study were recently released in which a newer Evodial dialyzer (Gambro-Hospal, Meyzieu, France) which contains a 'heparin-grafted' membrane was used and compared with 'standard care' which consisted of either an NS flush or predilution protocol. While the Evodial dialyzer outperformed the standard care arm, clotting still occurred in 33% of the treatments [5]. Combining two of the above heparin-sparing approaches, Francois et al. used the heparin-grafted Evodial dialyzer with citrate-enriched dialysate inpatients needing HD in the intensive care setting in which heparin was felt to be of increased risk. This strategy showed an improvement in treatment outcome with only 47 of 316 treatments (15%) requiring shortening of the treatment time related to various degrees of clotting of the dialysis circuit [15].

Anticoagulation-free HD utilizing NS flushes was reported in 1985 by Sanders et al. [16]. They looked at 28 patients receiving 158 HD sessions (5.6 treatments/patient). Most of these patients (23) were recent transplant recipients and could not receive heparin while the other five patients were postop following other surgeries. Prior to dialysis they flushed the dialyzer with 1 L of NS in which 3000 units of heparin was added, followed by a NS alone flush to remove any heparin-containing priming solution. During the treatment, they used blood flows up to 300 mL/min, and they flushed the dialyzer every 30 min with 100 mL of NS. They reported complete clotting of the dialyzer in 5% and partial clotting in another 6% of the treatments [16]. They felt that these results were similar to that reported at the time using low-dose and regional heparin protocols and concluded that HD without heparin was safe and tolerable. A study in 1987 by Schwab et al. reported their experience with HD without anticoagulation in 262 treatments in 49 patients (4.4 treatments/patient) [17]. Their protocol was similar to Sanders with a pretreatment heparin flush of the dialyzer with 5000 units in 1 L of NS and they utilized blood flows of up to 300 mL/min; however, they increased the frequency of the NS flushes (50–100 mL) to every 15 min. Two hundred and thirty-nine of the treatments were successfully completed while 23 required conversion to a low-dose heparin protocol. Circuit clotting occurred in 2% of the treatments [17]. A final anticoagulation-free HD study in 2004 by Stamatiadis et al. described their results of 1224 treatments in 266 patients (4.6 treatments/patient) considered at high risk for bleeding. Their results were not as successful with circuit clotting at 5%. However, their NS flushes during the treatment were only 50 mL/hour of NS and blood flows averaged <250 mL/min [18].

Our clotting rate of 1% was <2–5% described in the three aforementioned references. One possibility for these differences is that Schwab et al. [17] and Stamatiadis et al. [18] studied patients that were considered at high risk of bleeding while we used our heparin-free protocol on all inpatients regardless of their medical condition. Some of the high-risk patients in the other studies may have had recent trauma or surgery with associated inflammation

Table 2. Anticoagulation-free protocols using normal saline flushes

	Access blood flow (mL/min)	Saline flush regimen	Clotting (%)
Present study	>350	100 mL q15 min	1
Sanders et al. [16]	300	100 mL q 30 min	5
Schwab et al. [17]	300	50–100 mL q 15 min	2
Stamatiadis et al. [18]	<250	50 mL q 60 min	5

which may have increased the risk for clotting. From a protocol standpoint, our potentially lower rate of clotting may relate to the higher blood flow rate or the more aggressive NS flushing of the circuit that we employed in our protocol (Table 2). Another possibility for our results is the use of bloodlines in which there is no blood-air contact. And while these airless bloodlines were 'designed to reduce clotting and heparin' (http://www.henryschein.com/us-en/images/Dialysis/StreamlineBrochure.pdf) which makes intuitive sense, we were unable to find any clear objective evidence of this in the literature. However, these bloodlines have been shown to allow higher blood flow without increasing arterial resistance, improved KT/V and decreased heparin requirements compared with standard bloodlines [19]. If the bloodlines do play a role in our low rate of clotting, this may limit the applicability of our protocol, as they are manufactured and approved for the Fresenius 2008 and the B. Braun Dialog+ dialysis machines typically used in the USA, while these bloodlines are not manufactured or approved for use in other HD machines more typically used in Europe.

While 5% clotting may be acceptable in high-risk patients, 1% clotting makes this strategy very attractive to use as a default in all patients regardless of any underlying conditions that may make them 'high risk'. Any extra cost incurred from the NS administered during the treatment should be offset by the lack of heparin and not having to measure a patient's coagulation status during the treatment.

We arbitrarily picked the number of 400 treatments but decided that the information would be more valuable if we used only one treatment/patient as opposed to, for example, 400 treatments in 100 patients (4 treatments/patient) and so we opted for the first dialysis treatment of each patient's hospitalization.

Only 1% of treatments clotted. With such a low number, it is difficult to determine factors that may be associated with this event. Even with this limitation, circuit clotting appeared to be more common in treatments where there were problems with the access in which bloodlines were reversed and lower blood flow rates and higher arterial pressures were observed. This does not come as a surprise as these factors may contribute to access recirculation and hemoconcentration. The use of a catheter as an access was not statistically associated with circuit clotting, but this may be because clotting was so infrequent that this study was not powered to determine this effect. A functional access has always been the Achilles heel of dialysis and it rings true here as well. It therefore makes sense that this may be a modifiable risk factor for clotting when using an anticoagulation-free treatment protocol. However, nephrologists already try to provide a patient the best possible access as this also impacts clearance and the risk for thrombosis and infection. Thus, we suspect that improving the functionality of an access for this goal is naïve and fortunately, our clotting rate was so low that this may be a moot point anyway.

This was a retrospective data evaluation study. We did not have a control group of treatments that received anticoagulation during dialysis to know if there would be less clotting (<1%) if anticoagulation had been used. However, with an HD circuit clotting rate of only 1% in our anticoagulation-free treatments, it would not have been statistically significant even if we did have a control group of 400 anticoagulated treatments in which there was 0% clotting. If we doubled our sample size to 800 anticoagulation-free treatments and had the same 1% clotting rate, and were able to compare it with 800 anticoagulated treatments in which 0% clotting occurred, this would achieve statistical significance at $P = 0.01$, but one could question if this statistical significance is clinically significant or certainly worth the risks associated with anticoagulation. In that regard, we do not even know if our anticoagulation-free protocol is associated with fewer bleeding complications since we did not compare it with patients that were dialyzed with anticoagulation. The assumption is that the use of various anticoagulation protocols with dialysis is associated with bleeding or electrolyte abnormalities that our anticoagulation-free treatments avoid, but our data cannot comment on that. We can say however that there cannot be an anticoagulation-related bleeding or electrolyte complication when anticoagulation is not utilized. And since there appears to be no downside to using our anticoagulation-free approach for all inpatient dialysis treatments, we are comfortable recommending this as a default HD protocol strategy for all inpatients needing HD, regardless of their risk of bleeding.

While clotting was rarely seen with our protocol, we do not have data on dialyzer performance, and the lack of clotting does not mean that dialyzer clearance did not decrease, or at least more so using our protocol than had we used heparin. For example, when citrate-containing dialysate treatments were compared with standard dialysate treatments (both using similar systemic heparin protocols), clotting was not seen in either case, but the treatments associated with citrate had higher urea and other molecule clearances [8]. While the explanation for these findings are not known, it does imply that subclinical nonvisual changes within the dialyzer could affect its performance. The dialysis machines we use in the hospital do not measure KT/V, nor do we routinely measure urea reduction ratio on inpatients. The lack of this information is a limitation of our study and we may be compromising clearance by not using heparin [19]. However, it has been demonstrated in two studies that dialyzer clearances were similar in treatments that used heparin compared with those that did not use heparin [20, 21]. It is also possible that the improved KT/V that has been reported using Streamline bloodlines could counteract any potential changes in dialyzer function. It should also be noted that the role of 'adequacy' has been established primarily in the outpatient dialysis setting and its role in the inpatient setting is not well established.

We believe our data support our anticoagulation-free protocol utilizing high blood flows, frequent large volume NS flushes and even 'airless' bloodlines, as an excellent option for all adult inpatient HD treatments. This strategy appeared to be successful across all access types with essentially no clotting of the HD circuit. The effect of this regimen on dialyzer function is not known.

References

1. Cronin RE, Reilly RF. Unfractionated heparin for hemodialysis still the best option. *Semin Dial* 2010; 23: 510–515
2. Davenport A. What are the anticoagulation options for intermittent hemodialysis? *Nat Rev Nephrol* 2011; 7: 499–508
3. Chanard J, Lavaud S, Mahuet H *et al*. The clinical evaluation of low-dose heparin in haemodialysis: a prospective study using the heparin-coated AN 69 ST membrane. *Nephrol Dial Transplant* 2008; 23: 2003–2009
4. Evenepoel P, Dejagere T, Verhamme P *et al*. Heparin-coated polyacrylonitrile membrane versus regional citrate anticoagulation: a prospective randomized study of 2 anticoagulation strategies in patients at risk of bleeding. *Am J Kidney Dis* 2007; 49: 642–649
5. Laville M, Dorval M, ROs JF *et al*. Results of the HepZero study comparing heparin-grafted membrane and standard of care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis. *Kidney Int* 2014. doi:10.1038/ki.2014.225
6. Mujais S, Chimeh C. Heparin free hemodialysis using heparin coated hemophan. *ASAIO J* 1996; 42: M538–M541
7. Kessler M, Gangemi C, Martones AG *et al*. Heparin-grafted dialysis membrane allows minimal systemic anticoagulation in regular hemodialysis patients: a prospective proof-of-concept study. *Hemodialysis Int* 2013; 17: 282–293
8. Kossmann RJ, Gonzales A, Callan R *et al*. Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. *Clin J Am Soc Nephrol* 2009; 4: 1459–1464
9. Tu A, Ahmad S. Heparin-free hemodialysis with citrate-containing dialysate in intensive care patients. *Dial Transplant* 2000; 29: 620–624
10. Shen JI, Mitani AA, Chang TI *et al*. Use and safety of heparin-free maintenance hemodialysis in the USA. *Nephrol Dial Transplant* 2013; 28: 1589–1602
11. Holden RM, Harman GJ, Wang M *et al*. Major bleeding in hemodialysis patients. *Clin J Am Soc Nephrology* 2008; 3: 105–110
12. Bolliger D, Szlam F, Azran M *et al*. The anticoagulant effect of protamine is attenuated in the presence of platelets or elevated factor VIII concentrations. *Anesth Analg* 2010; 111: 601–608
13. Flanigan MJ, Von Brecht J, Freeman RM *et al*. Reducing the hemorrhagic complications of hemodialysis: a controlled comparison of low-dose heparin and citrate anticoagulation. *Am J Kidney Dis* 1987; 9: 147–153
14. Swartz RD. Hemorrhage during high-risk hemodialysis using controlled heparinization. *Nephron* 1981; 28: 65–69
15. Francois K, Wissing KM, Jacobs R *et al*. A retrospective cohort of heparin-free intermittent hemodialysis (IHD) combining heparin-coated AN69ST membranes (EVODIAL®) and citrate-enriched dialysate (Citrasate®) in an intensive care setting. *Nephrol Dial Transplant* 2013; 28: i418
16. Sanders PW, Taylor H, Curtis JJ. Hemodialysis without anticoagulation. *Am J Kid Dis* 1985; 1: 32–35
17. Schwab SJ, Onorato JJ, Sharar LR *et al*. Hemodialysis without anticoagulation. One-year prospective trial in hospitalized patients at risk for bleeding. *Am J Med* 1987; 83: 405
18. Stamatiadis DN, Helioti H, Mansour M *et al*. Hemodialysis for patients bleeding or at risk for bleeding can be simple safe and efficient. *Clin Nephrol* 2004; 62: 29–34
19. Haas L, Ahuja M. Improving hemodialysis adequacy, anticoagulation and dialyzer efficiency with streamline bloodlines. *J Am Soc Nephrol* 2010; 21: 435A
20. McGill R, Blas A, Bialkin S *et al*. Clinical consequences of heparin-free hemodialysis. *Hemodial Int* 2005; 9: 393–398
21. Casati S, Mioa M, Gransiani G *et al*. Hemodialysis without anticoagulants: efficiency and hemostatic aspects. *Clin Nephrol* 1984; 21: 102–105