Sonoclot coagulation analysis: new bedside monitoring for determination of the appropriate heparin dose during haemodialysis

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Abstract

Background. Thrombotic and haemorrhagic complications affect cardiovascular morbidity and mortality in haemodialysis patients. We investigated whether a new bedside Sonoclot analysis is useful for determining an appropriate heparin dose during haemodialysis.

Methods. Twenty-two haemodialysis patients (15 males and seven females) treated with unfractionated heparin were recruited. Sonoclot parameters, including activated clotting time (ACT), clot rate (CR), time to peak (TP) and peak amplitude (PA), were examined before and after haemodialysis, coupled with conventional coagulable variables, platelet count and fibrinogen level. Some indices were determined and verified to control heparin dose. Thrombotic and haemorrhagic complications were observed for 3 months. Sonoclot analysis was subsequently performed before initiation, 1 h later, 2.5 or 3 h later (before cessation of heparin infusion), and at the end of haemodialysis.

Results. Both CR and PA were positively correlated with platelet count and fibrinogen level. Sonoclot parameters except for PA were significantly correlated with heparin dose. Heparin dose was reduced without causing complications in 12 patients with ΔACT ≥40 s and/or CR after haemodialysis (CRpost) <20 U/min. Thrombotic complications occurred in five patients who had CRpost >30 U/min. ACT and TP increased during heparin treatment. ACT was reversed but TP did not change after cessation of heparin. CR significantly decreased after initiation of heparin and was reversed, although not completely, after cessation of heparin. PA showed no significant changes during haemodialysis.

Conclusions. Sonoclot analysis can monitor accurate coagulable states and determine an appropriate heparin dose during haemodialysis.

Keywords: coagulation; haemodialysis; heparin; Sonoclot analysis

Introduction

A coagulable state must be carefully monitored and controlled during haemodialysis treatment to prevent thrombotic and haemorrhagic complications, which greatly affect high cardiovascular morbidity and mortality in haemodialysis patients [1]. Hypo- and hypercoagulable complications occur due mainly to an inappropriate dose of heparin administered during dialysis. However, heparin treatment during haemodialysis remains empirical because of the need for immediate correction and the lack of availability of rapid intra-haemodialysis coagulation monitoring other than activated clotting time (ACT) at most institutions. Traditional coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, platelet count and specific factor assays, assess only isolated portions of the complex in the clotting cascade. A different aspect of the clotting process is measured in each of these tests, but a complete picture of the status of the coagulation system could not be obtained even if these tests were used in combination. Since these tests are also insensitive and time-consuming, they have limited appeal for the routine clinical laboratory.

Sonoclot analysis provides a rapid and complete evaluation of the overall haemostatic system, including the performance of the coagulation cascade and fibrin-platelet interaction [2,3]. In fact, Sonoclot analysis has been shown to be of clinical value in the evaluation of the haemostatic process during hepatic transplantation, cardiac surgery and other operations [4–6]. The aim of the present study is to investigate whether a new bedside Sonoclot analysis is useful for determining appropriate anticoagulation regimens during haemodialysis treatment.
Subjects and methods

Patients

This study was performed with the approval of the institutional ethical committee, and informed consent was received from all patients. Twenty-two haemodialysis patients (15 males and seven females) aged 39–80 years (mean age 63.5 ± 10.4 years) were recruited. The main clinical characteristics of the haemodialysis patients in this study are shown in Table 1. The mean duration of haemodialysis was 59.1 months. The underlying renal diseases of the haemodialysis patients were glomerulonephritis (n = 8), diabetes mellitus (n = 7), nephrosclerosis (n = 3) and other diseases (n = 4). All of the 22 patients had been treated with oral anticoagulation therapy. All of the patients had been receiving antiplatelet treatment. None of the patients had been receiving oral anticoagulation therapy. All of the patients were dialysed for 3–4 h per session using high-flux membranes (dialysis filter surface area 1.1–2.1 m²).

All of the patients received unfractionated heparin to prevent clotting of dialyser membranes and artificial surfaces of extracorporeal devices. The dose of heparin during haemodialysis had been determined earlier for each patient, aiming at APTT being 1.5- to 2.0-fold greater than the unheparinized baseline value. All of the patients had received the same dose of heparin for at least 1 month prior to the study. The initial load of unfractionated heparin (500–1500 IU) was infused by a bolus, and this was followed by a constant infusion of heparin at a rate of 500–1500 IU/h. Infusion was stopped 30 min before completion of haemodialysis treatment.

Protocol 1

Blood samples were drawn from an afferent cannula (arterialized blood) proximal to the addition of heparin and the dialyser membrane before initiation of heparin treatment and at completion of haemodialysis treatment. APTT (s), PT (%) and fibrinogen level (mg/dl) were measured using commercially available kits. Platelet count (counts/microlitre) was determined by automated cell counting in the course of performing routine full blood counts.

Whole blood coagulation was assessed using a Sonoclot Analyzer® (Sienco Inc., CO, USA) within 2 min of obtaining the blood sample. Immediately before analysis, a new plastic probe was inserted into the head, and the chart recorder was adjusted to the zero position. A pre-warmed (37°C) plastic cuvette containing powdered glass beads (as a contact activator) was placed into the instrument, and 0.4 ml of whole blood was pipetted into the cup. After ensuring proper mixing of the sample for 10 s, the probe was gently lowered into each sample by closing the head of the instrument, and a few drops of mineral oil (Sonoil®; Sienco Inc., CO, USA) were spread over the blood surface to prevent blood evaporation. The viscoelastic properties of clot formation were determined by impedance on a vibrating probe. An idealized Sonoclot graph is shown in Figure 1. The instrument automatically measures and displays whole blood ACT (s) and clot rate [CR (U/min)] of coagulation. Other parameters, time to peak [TP (min)] and peak amplitude [PA (U)], were determined manually from the recorder tracings.

Protocol 2

Based on the results of protocol 1, two indices were determined to try the reduction of heparin dose in patients expected to have an excess of heparin dose. The indices were ΔACT ≥40 s, defined as the mean of ΔACT+SEM (standard error of the mean), and CR after haemodialysis (CRpost) <20 U/min, defined as the mean of CRpost-SEM. For 3 months the indices were verified by the absence of the following criteria: coagulation of the dialyser during haemodialysis, retention of blood in the dialyser at the end of dialysis after rinsing with saline, and prolonged bleeding after haemodialysis.

Protocol 3

After the appropriate heparin dose had been determined for each patient based on the results of protocol 2, blood samples were drawn before initiation of haemodialysis and heparin treatment (time point A), at 1 h after the start of haemodialysis (B), at 2.5 or 3 h after the start of haemodialysis (C, when heparin infusion was not stopped), and at the end of haemodialysis treatment (D, at 30 min after cessation of heparin infusion). Sonoclot analysis was performed in all blood samples, and changes in Sonoclot parameters, including ACT, CR, TP and PA, were determined during haemodialysis treatment.

Statistical analysis

Numeric variables were expressed as means ± SD (standard deviation) for the characteristics of patients and as means ± SEM for the parameters of Sonoclot analysis. The difference between two dependent variables was analysed using the paired Student’s t-test. Spearman’s rank correlation test was used for analysis of correlations between two variables. Group statistical comparison was assessed by simple analysis of variance. A P value of <0.05 was considered statistically significant.

Table 1. Clinical characteristics of the haemodialysis patients (n = 22)

| Age (years) | 63.5 ± 10.4 |
| Gender (male/female) | 15/7 |
| Diagnosis |  |
| Glomerulonephritis | 8 |
| Diabetes mellitus | 7 |
| Nephrosclerosis | 3 |
| Others | 4 |
| Duration of dialysis (months) | 59.1 ± 13.8 |
| Systolic blood pressure (mmHg) | 147 ± 26 |
| Diastolic blood pressure (mmHg) | 76 ± 11 |
| Pulse rate (beats/min) | 69 ± 8 |
| Kr/V | 1.22 ± 0.32 |
| Drug therapy |  |
| Erythropoietin | 22 (100%) |
| Antiplatelet drug | 7 (32%) |
| Anticoagulation drug | 0 (0%) |

Values, where applicable, are represented as mean ± SD.
Results

Protocol 1

Results are shown in Table 2. Both CR and PA were positively correlated with platelet count and fibrinogen level before and after haemodialysis. After haemodialysis and heparin treatment, ACT and TP significantly increased, whereas CR significantly decreased. APTT was correlated positively with ACT and negatively with CR only after haemodialysis. Total and dry weight-corrected heparin doses showed significant linear correlations with changes during haemodialysis in ACT ($r=0.70$, $P<0.01$ and $r=0.69$, $P<0.01$, respectively), CR ($r=-0.65$, $P<0.01$ and $r=-0.61$, $P<0.01$, respectively) and TP ($r=0.44$, $P<0.05$ and $r=0.50$, $P<0.05$, respectively), but not with changes in PA. PA but not other Sonoclot parameters before haemodialysis were significantly elevated in diabetic patients compared with those in non-diabetics. Three diabetic patients who had past histories of thromboembolism showed PA of >100 U.

There were no significant differences in any of the Sonoclot variables between patients who received antiplatelet therapy and those who did not.

Protocol 2

The reduction in heparin dose was safely performed in 12 patients with $\Delta\text{ACT} >40$ s and/or CRpost $<20$ U/min. During the 3-month follow-up period...

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### Table 2. Values and correlations of Sonoclot variables

<table>
<thead>
<tr>
<th>Value (means±SEM)</th>
<th>Correlation coefficient (r value)</th>
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<tbody>
<tr>
<td></td>
<td>APTT (s)</td>
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<td>Before haemodialysis</td>
<td>ACT (s)</td>
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<td>CR (U/min)</td>
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<td>TP (min)</td>
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<td>PA (U)</td>
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<sup>a</sup>$P<0.01$; <sup>b</sup>$P<0.05$; <sup>c</sup>$P<0.05$ vs pre-haemodialysis; <sup>d</sup>$P<0.01$ vs pre-haemodialysis.

ACT = activated clotting time, CR = clot rate, TP = time to peak, PA = peak amplitude, APTT = activated partial thromboplastin time, PT = prothrombin time.
there was no coagulation of the dialyser, retention of blood in the dialyser, or prolonged bleeding after haemodialysis for any of these 12 patients. On the other hand, coagulation of the dialyser or retention of blood in the dialyser after haemodialysis treatment occurred during the observation period in five of the 22 patients. CR_post in all of these five patients was >30 U/min. Heparin dose was subsequently increased in these patients, and CR_post was adjusted appropriately to within a range of 20–30 U/min. ΔACT and CR_post in the remaining five patients were <40 s and 20–30 U/min, respectively, and no thrombotic or haemorrhagic complications were observed during the follow-up period.

**Protocol 3**

The time course of each Sonoclot variable in appropriate heparin dose is shown in Figure 2. ACT gradually increased during heparin treatment (time points A to C) and rapidly decreased after cessation of heparin treatment (time points C to D). There was no significant difference between the values of ACT at time points A and D. CR significantly decreased after initiation of heparin treatment and was promptly reversed, but not completely, after cessation of heparin treatment. There was a significant difference between the values of CR at time points A and D. TP significantly increased after initiation of heparin treatment but did not significantly change after cessation of heparin treatment. PA showed no significant changes during haemodialysis and heparin treatment.

The Sonoclot variables before haemodialysis in protocol 3 were comparable to those in protocol 1, performed 3 months before protocol 3, and each of the variables before haemodialysis in protocols 1 and 3 showed high reproducibilities and significant correlations as follows: ACT \( r = 0.45, P = 0.05 \), CR \( r = 0.82, P = 0.01 \), TP \( r = 0.57, P = 0.01 \), and PA \( r = 0.44, P = 0.05 \).

**Discussion**

Hypercoagulability is thought to occur in renal diseases, and possible mechanisms have recently been reviewed [7,8]. Patients undergoing chronic haemodialysis treatment are also at high risk for thromboembolic complications because they are exposed to additional exogenous factors that have an impact on their coagulation system. Therefore, determination of appropriate heparin therapy for patients undergoing haemodialysis is important for dialysis efficacy and reduction of thrombotic or haemorrhagic risks.

The heparin doses in our patients had been based on standard regimens modified empirically. The results in protocol 2 suggest that commonly used heparin doses determined by APTT are likely to be insufficient to effectively prevent thrombotic or haemorrhagic complications.

The Sonoclot signature gives a more comprehensive overview of the clotting cascade as a process. The possible advantages of Sonoclot analysis are as follows: (i) only a small specimen volume is needed;
The index of CRpost in patients expected to have an excess of heparin dose criteria seem to be useful for reducing heparin dose of the 22 patients based on these criteria. These of heparin dose was safely performed in 12 (54.5%) D points A and D. CRpost is considered to be more of CR, but not between the values of ACT, at time there was a significant difference between the values appropriate heparin dose had been determined, complications occurring in the future. After the use of antiplatelet drugs such as low-dose aspirin for prevention of myocardial infarction and stroke has been demonstrated, and this has resulted in an increasing number of patients receiving antiplatelet therapy. Seven (32%) of the 22 patients in this study received antiplatelet therapy. No significant differences in any of the Sonoclot variables were found between patients who received antiplatelet therapy and those who did not. It was previously reported that

Sonoclot analysis did not enable the effects of aspirin in normal volunteers to be determined [13]. Sonoclot analysis may be insensitive to the effect of antiplatelet treatment on platelet function, but not that on platelet count.

Several limitations of this study must be considered. First, our study is limited in terms of the number of patients examined, and it is important to confirm the findings with larger studies. Secondly, since the follow-up period in this study was only 3 months, we could not assess thrombotic complications other than coagulation of the dialyser. Therefore it is necessary to investigate other thrombotic complications in a long-term follow-up study. Thirdly, in the present study, heparin was first infused by a bolus and then infused at a constant rate until 30 min before completion of haemodialysis treatment. An appropriate range of CRpost may be different in other prescriptions of heparin treatment. However, CR seems to be useful because of its sensitivity to changes in heparin treatment.

In conclusion, heparin therapy in patients can be monitored during haemodialysis treatment by bedside Sonoclot analysis. CR at completion of haemodialysis treatment is particularly useful for monitoring heparin dose, and an appropriate CRpost for determining heparin dose during haemodialysis is within the range of 20–30 U/min.

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