Anticoagulation during haemodialysis using a citrate-enriched dialysate: a feasibility study

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Abstract

Background. The feasibility of anticoagulating the extracorporeal circuit during haemodialysis using a simple citrate-enriched dialysate was evaluated in a prospective, randomised, cross-over study of 24 patients who were at high risk for bleeding.

Methods. A dialysate, with a citrate level of 3 mEq/L (1 mmol/L), was generated by adding citrate to the conventional bicarbonate concentrate of a regular, dual-concentrate, bicarbonate-buffered dialysate delivery system. Each of the 24 patients received two dialysis treatments. For anticoagulation of the extracorporeal circuit, one treatment used the citrate-enriched dialysate (Citrate Group), while the other treatment used conventional saline flushing (Saline Group). The order of the two treatments was randomised. With either method, a heparinized, saline-rinsed dialyser was used, and no heparin was administered during dialysis.

Results. Ninety-two per cent (22 out of 24) and 100% of patients tolerated the procedure well in the Citrate Group and the Saline Group, respectively. Eight per cent (two out of 24) of the treatments in each group had to be abandoned because of clotting in the extracorporeal circuit. Significantly less thrombus formation in the venous air traps was detected in the Citrate Group. No patients from either group suffered from hypocalcaemic or bleeding complications, but the immediate post-dialysis and 0.5-h post-dialysis plasma levels of ionised calcium and of magnesium were slightly lower in the Citrate Group than in the Saline Group.

Conclusions. Our findings suggest that it is feasible to use the present simple citrate-enriched dialysate to dialyse patients safely and effectively. Furthermore, the approach is much simpler than a conventional, intermittent, saline-flushing method.

Keywords: anticoagulation; bicarbonate concentrate; citrate; dialysate; haemodialysis

Introduction

Bleeding complications in patients on chronic haemodialysis (HD) is a serious problem requiring special, often complicated and unreliable anticoagulation methods. Regional anticoagulation of the dialysis filter using either heparin-protamine or citrate-calcium infusions are difficult in balancing the two infusions used with either method. Similarly, periodic saline flushing is demanding of personnel time and reduces the efficiency of the dialysis that has to be stopped frequently.

Ahmad et al. were the first to regionally anticoagulate the dialyser using a special ‘acid concentrate’ made by replacing, with citric acid, the acetic acid of a conventional ‘acid concentrate’. The dialysate had a citrate level of 2.4 mEq/L (0.8 mmol/L) [1–4]. This citrate-enriched ‘acid concentrate’ is now commercially available in either a powder form or a liquid form (called DRYalysate® and Citrasate®, respectively) [Advanced Renal Technologies Inc, www.citrasate.com]. It is believed that the citrate in the dialysate can reach across the dialyser membrane to chelate calcium in the blood within the dialyser and the venous tubing, thus impairing the clotting process to bring about regional anticoagulation [4]. The dialysate citrate concentration used by Ahmad and associates is only about one-third to one-sixth of the plasma citrate level that is required for regional anticoagulation achieved by systemic citrate infusion [5]. Recently, the use of a dialysate with a citrate level of 4 mEq/L (1.3 mmol/L) for the purpose of regional anticoagulation has also been described [6].

Ahmad’s citrate-enriched dialysate has been found to reduce clotting in the extracorporeal circuit so much so that the administration of heparin could be curtailed or even abolished [1,6]. If used with a full dose of heparin, this dialysate has been reported to improve dialysis efficiency with higher values of Kt/Vurea, allow more reuse of dialysers, promote removal of phosphorus, aluminium and beta2-microglobulin and improve haemodynamics with a
lower systemic blood pressure through a reduction of peripheral resistance [2–4,7].

In the present study, instead of using a specially manufactured, citric acid-containing ‘acid concentrate’ for the purpose of regional anticoagulation, we chose to simply add citrate into a conventional ‘bicarbonate concentrate’ for the anticoagulation [8]. To our knowledge, the simple addition of citrate to a ‘bicarbonate concentrate’ for the aim of anticoagulating an extracorporeal circuit has not been done before.

We evaluated the feasibility of using our new citrate-enriched dialysate to dialyse end-stage renal disease (ESRD) patients with a high risk of bleeding. The effect was compared with a conventional intermittent saline-flushing method in the same patients. Preliminary results have been presented [9].

Materials and methods

ESRD patients requiring HD treatments at the Alice Ho Miu Ling Nethersole Hospital in Hong Kong, China, were screened. Patients with high or very high bleeding risks determined by Swartz criteria [10] and ≥18 years old were recruited to participate in the study. Patients with plasma albumin-adjusted calcium levels <3.8 mEq/L (1.9 mmol/L) were excluded. The study protocol was approved by the Ethics Committee of the hospital. The study fully adhered to the Declaration of Helsinki, and all patients gave both oral and written consents.

The HD sessions were carried out using Fresenius 4008S haemodialysis machines (Fresenius Medical Care, Bad Homburg, Germany) and conventional, polyamide, hollow-fibre dialysers (Polyflux 8L™, Dialysatoren GmbH & Co., Hechingen, Germany). Being a low-flux dialyser, the Polyflux 8L provides a urea (MW 60 Da) clearance of 190 mL/min and a vitamin B12 (MW 1355 Da) clearance of 96 mL/min, both in the face of dialyser blood and dialysate flow rates (mL/min) of 200 and 500, respectively. A fresh dialysate was used for each treatment. Prior to use, each dialysate was rinsed with 1 L of physiological saline containing 3000 units of heparin, followed by rinsing with 0.5 L of heparin-free physiological saline. A fresh dialysate was used for each treatment. Prior to use, each dialysate was rinsed with 1 L of physiological saline containing 3000 units of heparin, followed by rinsing with 0.5 L of heparin-free physiological saline. Regular bicarbonate-buffered dialysates were used and prepared by utilizing a dual-concentrate, bicarbonate-buffered dialysate delivery system that mixed product water with a conventional, liquid ‘bicarbonate concentrate’ (B Braun HD-1B, B Braun Medical Industries S/B, Penang, Malaysia) and a conventional, liquid ‘acid concentrate’ (B Braun 3A, B Braun Medical Industries S/B) in a dilution ratio of 34:183:1 [11]. The bicarbonate-buffered dialysates so produced had the following composition (in mEq/L): sodium 140, calcium 2.5, magnesium 1, potassium 2, bicarbonate 3.5, chloride 107 and acetate 4. There was no dextrose in this dialysate.

The patients were randomised to receive a 4-h HD treatment using either the present citrate-enriched dialysate technique (Citrate Group) or a conventional intermittent saline-flushing approach (Saline Group). For the following HD session, the opposite anticoagulation method was employed. During dialysis, no systemic heparin was given in either group. Randomisation was carried out by drawing a consecutively numbered, sealed, opaque envelope containing a form indicating which anticoagulation procedure the patient would receive. The envelopes were numbered in accordance with a randomisation table. For the Citrate Group, the citrate-enriched dialysate was prepared by introducing 2.17 L of a ‘bicarbonate concentrate’ into a conventional, liquid dialysate containing 10-L aliquot of the above-mentioned, conventional, liquid dialysate (Polyflux 8L™, Dialysatoren GmbH & Co., Hechingen, Germany). Being a low-flux dialyser, the Polyflux 8L provides a urea (MW 60 Da) clearance of 190 mL/min and a vitamin B12 (MW 1355 Da) clearance of 96 mL/min, both in the face of dialyser blood and dialysate flow rates (mL/min) of 200 and 500, respectively. A fresh dialysate was used for each treatment. Prior to use, each dialysate was rinsed with 1 L of physiological saline containing 3000 units of heparin, followed by rinsing with 0.5 L of heparin-free physiological saline. Regular bicarbonate-buffered dialysates were used and prepared by utilizing a dual-concentrate, bicarbonate-buffered dialysate delivery system that mixed product water with a conventional, liquid ‘bicarbonate concentrate’ (B Braun HD-1B, B Braun Medical Industries S/B, Penang, Malaysia) and a conventional, liquid ‘acid concentrate’ (B Braun 3A, B Braun Medical Industries S/B) in a dilution ratio of 34:183:1 [11]. The bicarbonate-buffered dialysates so produced had the following composition (in mEq/L): sodium 140, calcium 2.5, magnesium 1, potassium 2, bicarbonate 3.5, chloride 107 and acetate 4. There was no dextrose in this dialysate.

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Patients were observed closely for manifestations of hypocalcaemia, such as paraesthesia, muscle cramps, hypotension and cardiac arrhythmias. Continuous electrocardiogram (EKG) monitoring was performed throughout the dialysis sessions. Peripheral venous blood samples were taken for ionised calcium (iCa) determinations whenever a patient developed any abnormal signs and/or symptoms.

Thrombus formation visualized in the dialyser and in both the arterial and venous air traps was estimated at the end of dialysis by three different observers. The latter were blinded to the method of anticoagulation and, for the

| Table 1. Compositions of the dialysate after adjustment of the sodium and bicarbonate-control switches |
|---|---|
| Sodium | 137<sup>b</sup> | 138<sup>c</sup> |
| Chloride | 104 | 103 |
| Calcium | 2.3 | 2.3 |
| Magnesium | 1.0 | 1.1 |
| Potassium | 1.9 | 1.9 |
| Dextrose | 0 | 1.2 (mmol/L) |
| Bicarbonate | 36 | 31<sup>c</sup> |
| Acetate | 4.0 | 4.0 (approximately; not measured) |
| Citrate | 0 | 3.1 (1 mmol/L) |

Values shown are expressed in mEq/L except for dextrose which is expressed in mmol/L. All values were determined by our clinical chemistry laboratory except for acetate which was obtained from the manufacturer's brochure. The true values of acetate in the dialysates will be slightly different from the level of 4 mEq/L due to the presence of dilution or other factors mentioned below.


<sup>a</sup>For the saline method, the sodium-control switch of the dialysis machine was dialled downward so that the dialysate sodium level would come down from the original value of 140 to one of 137 mEq/L.

<sup>b</sup>For the citrate method, sodium level in B' is lower than that in B because the sodium level in ACD-A is lower than that in B. Therefore, the sodium-control switch of the dialysis machine was dialled upward so that the dialysate sodium level would come up from the original value of 130 to one of 138 mEq/L. Bicarbonate level in B' is lower than that in B because there is no bicarbonate in ACD-A. Therefore, the bicarbonate-control switch was also dialled upward so that the dialysate bicarbonate level would come up from a value of 28 to one of 31 mEq/L.

By adjusting the sodium- and the bicarbonate-control switches, the proportioning ratio of the ‘bicarbonate concentrate’ and the ‘acid concentrate’ used during the preparation of the dialysate will vary slightly from the norm, thus altering the concentrations of the ingredients. However, apart from bicarbonate, the levels of some of the other original constituents in the two dialysates, e.g. chloride, calcium, magnesium and potassium, happened to be not too far apart in the present study. Some differences were too small to be detected by our laboratory methods.
assessment of clotting, used a 0 to 4 scale (grade 0: no detectable clotting, grade 1: minimal clot formation, grade 2: moderate clot formation, grade 3: major clot formation but dialysis still possible and grade 4: complete occlusion of dialyser or of an air trap, rendering dialysis impossible).

Pre-dialysis blood samples were collected according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [13]. For patients who were dialysed using venous catheters, the pre-dialysis blood samples were taken after having withdrawn 20 mL of blood to minimize problems of saline and heparin dilution. The immediate post-dialysis blood specimens were sampled using the K/DOQI slow-blood-flow method [13]. For patients who were dialysed using an arteriovenous access, the arterial line needle was left in place after the HD treatment for the sampling of the 0.5-h post-dialysis blood, with the specimen taken only after 20 mL of blood had first been withdrawn. For patients who were dialysed using a central venous catheter, the 0.5-h post-dialysis blood specimen was obtained from a peripheral vein. Plasma levels of urea, creatinine, sodium, iCa, magnesium and bicarbonate (the last determined by a blood gases analysis method), were determined in all the samples. Levels of haemoglobin, haematocrit, platelet count, prothrombin time and activated partial thromboplastin time were determined in the pre-dialysis blood samples. Dialyser urea and creatinine clearances were estimated by simultaneously obtaining blood samples from the pre- and post-dialyser sampling ports, at the start and at the end of each treatment, after having kept the ultrafiltration rate at zero prior to blood sampling. The dialyser clearance values were derived by using the following formula:

\[
\text{Dialyser clearance, mL/min} = \frac{Q_b(1-Hct) \times (C_{in} - C_{out})}{C_{in}}
\]

where \(Q_b\) represented the blood flow rate (mL/min); \(Hct\), haematocrit; \(C_{in}\), the concentration of solute entering the dialyser; \(C_{out}\), the concentration of solute exiting the dialyser.

Urea reduction ratio (URR) was calculated using a standard equation [14].

Statistical evaluations were performed by using the SPSS version 13.0 software package (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD. Comparisons between the two groups were made by using the chi-square test or the Fisher’s exact test for categorical data when appropriate; and the paired Student’s t-test for parametric data. All reported P-values are two-sided. A P-value of less than 0.05 is considered statistically significant.

**Results**

Twenty-four patients participated in the study. Patient characteristics are shown in Table 2. Of these, 20 patients were at high risk of bleeding due to recent surgeries, and four patients had a history of recent haemorrhage (wound, gastrointestinal and haemorrhagic liver cyst). Five out of the 24 patients were receiving aspirin (80 mg daily) for the prophylaxis of myocardial infarction. None of the patients received any oral anticoagulant therapy. Baseline parameters of the two groups were closely similar (Table 3). No bleeding was noted during or after the dialysis sessions in either group. Blood transfusion was required during two treatments (8%) in each group. The ultrafiltration volume was significantly higher in the Saline Group (3.0 ± 0.9 L versus 1.4 ± 0.7 L; \(P < 0.0001\)) due to the need for removal of the infused saline.

Among patients in the Citrate Group, one had hypotension 3.2 h after the start of dialysis, and another had hypotension and leg cramps 3.5 h after the start of dialysis. Both patients responded to saline administration. In both patients, plasma iCa levels were found to be 2 mEq/L (1 mmol/L) at the time of the symptoms, and EKGs did not show any evidence of hypocalcaemia. Consequently, it was thought that the symptoms were not citrate-related. With regard to blood pressure, baseline systolic and mean pressures were higher in the Citrate Group during the first hour of dialysis. However, after the first hour, blood pressure readings for the two groups were similar (Figure 1). No patients suffered from hypocalcaemic manifestations, and the EKGs of all the patients were unremarkable during dialysis.

Dialyser performance was depicted in Table 4. Two treatments (8%) in each group had to be abandoned on account of clotting in the extracorporeal circuit. With respect to the two treatments from the Citrate Group, the circuit clotted after 3.2 and 3.8 h of HD treatment, respectively. In the case of the Saline Group, the circuit clotted after 2 and 3.6 h of HD treatment, respectively. Of these episodes of clotting, one patient had the circuit clotted when being dialysed both as a member of the Citrate Group and as one of the Saline Group. A significantly lower score of thrombus formation in the venous air traps was observed in the Citrate Group (Table 4).

Twenty-two out of 24 patients (92%) completed the 4-h dialysis treatment in each group. The reductions in dialyser urea clearance as a result of a dialysis treatment were comparable in the two groups (–6.5 ± 4.8% for the Citrate Group versus –7.8 ± 5.1% for the Saline Group; \(P = ns\)). Similar reductions in dialyser creatinine clearance were also observed (–7.3 ± 4.5% for the Citrate Group versus –9.3 ± 6.4% for the Saline Group; \(P = ns\)). The URR values for the two groups were comparable (67.5 ± 5.6% versus 66.4 ± 5.8%; \(P = 0.050\)). The results of the blood tests obtained before dialysis, immediate post-dialysis and 0.5 h post-dialysis are presented in Table 5. Baseline plasma magnesium level was significantly higher in the Citrate Group. There was no difference in plasma sodium levels at the end of dialysis and 0.5 h post-dialysis in both groups. For the Citrate Group, the plasma levels of iCa, magnesium and bicarbonate were significantly lower at the end of dialysis and 0.5 h post-dialysis. The plasma levels of iCa did not return to baseline 0.5 h after the termination of dialysis in both groups. In the Citrate Group, the plasma levels of iCa were significantly higher 0.5 h after dialysis treatments when compared to the immediate post-dialysis values.

**Discussion**

The results of our study suggest that it is feasible to prepare a citrate-enriched dialysate by introducing a solution...
of sodium citrate and citric acid to the liquid ‘bicarbonate concentrate’ of a dual-concentrate, bicarbonate-buffered dialysate delivery system. That the use of our citrate-enriched dialysate resulted in a lesser degree of thrombus formation in the venous air traps when compared to the use of a saline-flushing technique suggests the presence of a better anticoagulant effect at the dialyser level. The citrate method was much simpler to use than the saline method because the latter required stopping blood flow and the intermittent infusion of saline followed by the obligatory removal via ultrafiltration of an amount of fluid equal in volume to the saline introduced. The saline-flushing approach is time-consuming, complicated and labour-intensive [15].

Our data also suggest that HD using a citrate-enriched dialysate prepared by the present approach is safe. Patients generally tolerated such HD treatments well, and no patients were affected by hypercalcaemia-related symptoms, hypernatraemia or metabolic alkalosis. The immediate post-dialysis and 0.5-h post-dialysis iCa and magnesium levels were lower in the Citrate Group than in the Saline Group. However, the absolute values of the differences were minute (0.12 to 0.19 mEq/L for plasma iCa and 0.07 to 0.1 mEq/L for plasma magnesium) and, hence, not clinically significant. Such transient lowering of iCa levels has also been described by Ahmad’s group [2]. By using a citrate level of 2.4 mEq/L in the dialysate, the latter group found that the post-dialysis iCa concentration had fallen by only 0.34 mEq/L. Such a small fall is consistent with our own finding of a reduction of 0.35 mEq/L. The lower post-dialysis iCa levels in the Citrate Group might be related to the utilization of iCa to form calcium/citrate complexes in the blood. On the other hand, the fall in iCa after dialysis might have been the result of a calcium loss to the dialysate if the dialysate ionised calcium level is lower than that in the plasma; the dialysate ionised calcium levels might have been low because of the formation of calcium/citrate complexes in the dialysate. Further studies are required to determine which of the above possibilities is the main cause for this decrease in post-dialysis iCa level. The higher 0.5-h post-dialysis iCa level is probably the result of the dissipation of citrate from the calcium/citrate complexes through metabolism, thus liberating iCa to approach its original level. The 0.44 mEq/L fall in post-dialysis plasma magnesium concentration is probably related to the interplay among plasma ionised magnesium, plasma magnesium/citrate complex, dialysate ionised magnesium and dialysate magnesium/citrate complex. Further studies are needed to shed light on this particular issue.

The relatively low dialysate level of bicarbonate used in the Citrate Group is probably responsible for the lower post-dialysis plasma bicarbonate values.

In the present study, we employed, as a source of citrate, the parenteral ACD-A preparation because of its frequent use as an anticoagulant in blood-side regional anticoagulation methods [16]. Since this ACD-A solution is relatively expensive, we envisage its replacement by a less costly non-parenteral preparation of: (i) sodium citrate [11], (ii) citric acid, or (iii) a combination of sodium citrate and citric acid. The use of such an inexpensive preparation can certainly lower the cost of a citrate-enriched dialysis treatment (Table 6).

The present study has some limitations. Firstly, the mean haematocrit value of our patients was relatively low. As haematocrit level has been reported to influence the clot-
Haemodialysis using citrate-enriched dialysate

Table 5. Biochemical data from patients who completed the 4-h HD in both the Citrate and the Saline Groups (n = 21)

<table>
<thead>
<tr>
<th></th>
<th>Start of dialysis</th>
<th>End of dialysis</th>
<th>0.5 h post-dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate Group</td>
<td>136.4 ± 2.7</td>
<td>135.5 ± 1.8</td>
<td>135.1 ± 1.6</td>
</tr>
<tr>
<td>Saline Group</td>
<td>136.1 ± 4.2</td>
<td>135.5 ± 2.6</td>
<td>135.2 ± 2.4</td>
</tr>
<tr>
<td>P-value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Ionised calcium, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate Group</td>
<td>2.28 ± 0.19a</td>
<td>1.93 ± 0.10b</td>
<td>2.00 ± 0.12c</td>
</tr>
<tr>
<td>Saline Group</td>
<td>2.23 ± 0.22ad</td>
<td>2.11 ± 0.12c</td>
<td>2.12 ± 0.12c</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Bicarbonate, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate Group</td>
<td>23.2 ± 2.8</td>
<td>26.6 ± 1.8</td>
<td>26.1 ± 2.2</td>
</tr>
<tr>
<td>Saline Group</td>
<td>22.1 ± 2.4</td>
<td>29.7 ± 2.9</td>
<td>29.9 ± 3.1</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Magnesium, mEq/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrate Group</td>
<td>1.72 ± 0.29</td>
<td>1.28 ± 0.10</td>
<td>1.32 ± 0.12</td>
</tr>
<tr>
<td>Saline Group</td>
<td>1.62 ± 0.27</td>
<td>1.39 ± 0.11</td>
<td>1.39 ± 0.12</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. ns, non-significant.

a versus c, P < 0.0001.
b versus c, P = 0.004.
d versus f, P = 0.002.
e versus f, P = ns.

Notes of extracorporeal blood circuits (the higher the haematocrit level, the higher the risk of clotting), caution should be taken in extrapolating the anticoagulation effect of the present citrate-enriched dialysate to HD patients with higher haematocrit levels. Should the present dialysate citrate level be inadequate for the purpose of anticoagulation in a particular patient and should there be no contraindications to the use of systemic heparin, a small dose of heparin can always be added as suggested by Ahmad and co-workers [6]. Secondly, in some countries, introducing chemicals to preformed dialysate concentrates is not allowed, whereas in the USA, such a practice is permitted. However, if such self-administration is not possible, citrate can be incorporated into ‘bicarbonate concentrates’ at the time of manufacture.

In conclusion, our data suggest that it is feasible to add citrate to the ‘bicarbonate concentrate’ of a conventional, dual-concentrate, bicarbonate-buffered dialysate delivery system to produce a citrate-containing dialysate. Using this citrate-enriched dialysate, it was possible to anticoagulate the extracorporeal circuit in a safe and simple manner. Our approach is at least as effective in terms of anticoagulation as an intermittent, saline-flushing technique. When compared to the latter method, the present approach is also easier to perform and capable of lessening substantially the workload of dialysis personnel. Finally, for the present purpose of regional anticoagulation, we surmise that sodium citrate alone or citric acid alone may work just as well as a combination of sodium citrate and citric acid. We also surmise that changes involving a conventional acid concentrate in the form of: (i) addition of sodium citrate, (ii) substitution of calcium chloride by calcium citrate and/or (iii) replacement of magnesium chloride by magnesium citrate, can all probably bring about results similar to those of the present study.

Table 6. Costs of ‘acid concentrate’ and ‘bicarbonate concentrate’ for preparing 120 L of a citrate-containing dialysate

<table>
<thead>
<tr>
<th></th>
<th>Ahmad's method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Present method&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid concentrate, US dollars/L</td>
<td>2.77–3.30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.96</td>
</tr>
<tr>
<td>Bicarbonate concentrate, US dollars/L</td>
<td>0.8</td>
<td>1.95 (ACD-A + ‘bicarbonate concentrate’)</td>
</tr>
<tr>
<td>Cost for making 120 L of a citrate-containing dialysate, US dollars&lt;sup&gt;c&lt;/sup&gt;</td>
<td>13.81–15.53</td>
<td>14.77</td>
</tr>
</tbody>
</table>

Note: Citrasate® = a proprietary name for a special citric acid-enriched ‘acid concentrate’.

ACD-A = anticoagulant citrate dextrose-solution-formula A (USP).

<sup>a</sup>The dialysate citrate level is 2.4 and 3.0 mEq/L in Ahmad's method and in the present method, respectively.
<sup>b</sup>In the USA, the cost per container housing 3.785 L (1 gallon) varies from 10.5 to 12.5 US dollars (depending on the location) if one orders 192 containers (information obtained on 25 May 2010 from DIAL MEDICAL SUPPLY, http://www.dialmedsupply.com). The cost increases as the quantity ordered decreases (information obtained from the above company’s brochure dated 1 November 2007).
<sup>c</sup>Since ‘bicarbonate concentrates’ are relatively inexpensive, the difference in cost between a ‘bicarbonate concentrate’ geared for use in the 34:1.83:1 dilution approach and one geared for use in the 42.28:1.72:1 dilution approach is negligible.

Acknowledgements. This study was supported by a Hong Kong Society of Nephrology Research Grant. The authors wish to thank the nursing staff, particularly Esther Siu-Chun Ng, Amy Lai-Ching Cheung, Queenie Wing-Yi Fok, Wing-Ki Chan and Flora Sau-Yung Wong, of the Dialysis Unit at the Alice Ho Miu Ling Nethersole Hospital for their dedicated assistance. The strong support of the present project by Mr. Rod S. Kenley is also greatly appreciated.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or in part, except in abstract formats.

Appendix

Composition of the conventional ‘bicarbonate concentrate’ used: (B)
Sodium 1307.1 mEq/L, chloride 521.4 mEq/L, bicarbonate 785.7 mEq/L.

Composition of the conventional ‘acid concentrate’ used: (A)
Sodium 2759.5 mEq/L, potassium 72.8 mEq/L, calcium 92.2 mEq/L, magnesium 36.8 mEq/L, chloride 2961.3 mEq/L, acetate acid 147.5 mmol/L, dextrose 0.

Composition of the ACD-A solution:
Sodium 224.4 mEq/L, citrate 224.4 mEq/L, citric acid 38 mmol/L, dextrose 123.7 mmol/L (12).

Composition of the new ACD-A-enriched ‘bicarbonate concentrate’ obtained by mixing 10 L of bicarbonate concentrate (B) with 2.17 L of ACD-A: (B’): Sodium 1114 mEq/L, chloride 428.4 mEq/L, bicarbonate 625.3 mEq/L<sup>*</sup>, citrate 60.3 mEq/L (40 mEq/L from sodium citrate; 20.3 mEq/L from citric acid), dextrose 22.1 mmol/L.

<sup>*</sup>Value remaining after the loss of bicarbonate through titration with the citric acid present in the ACD-A solution.
Effects of unfractioned heparin and low-molecular-weight heparin on osteoprotegerin and RANKL plasma levels in haemodialysis patients

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Abstract

Background. This randomized crossover study investigated the effects of unfractioned heparin (UFH) and low-molecular-weight heparin (LMWH) on intra- and post-dialytic blood levels of osteoprotegerin (OPG), receptor activator of nuclear factor kappa B ligand (RANKL) and inflammatory cytokines.

Methods. Forty patients on haemodialysis for at least 12 months were selected. UFH or LMWH was randomly assigned and maintained for 1 month, and then, in the following month, each patient was switched to the other form of heparin. In the mid-week session, we determined the changes in anti-Xa activity, OPG, RANKL, IL-1β, IL-6 and TNF-α values before heparin administration and after 15 min, 4, 8 and 24 h (T0, T1, T2, T3 and T4 respectively).

Since these parameters at the various experimental times showed a non-normal distribution, log transformation was applied in order to run parametric ANOVA, with Bonferroni correction for multiple comparisons.

Results. The changes in anti-Xa activity over time were similar but not the same for the UFH and LMWH. A highly significant (P < 0.001) increase in anti-Xa activity was detected at T1, regardless of the type of heparin, as confirmed in the comparison of T0 vs T1 using one-way ANOVA. Moreover, with both heparins, significant differences were found in the comparisons of anti-Xa activity at T1 vs T2 (both P < 0.001) and at T2 vs T3 (P = 0.0003 with UFH; P < 0.001 with LMWH). Conversely, the difference in anti-Xa activity at T3 vs T4 was still significant with UFH (P = 0.0186) but not significant with LMWH (P = 0.728). When