ORIGINAL ARTICLE

Efficacy of enoxaparin in preventing coagulation during high-flux haemodialysis, expanded haemodialysis and haemodiafiltration

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ABSTRACT

Background. Low-molecular-weight heparins (LMWHs) are easily dialysable with high-flow membranes; however, it is not clear whether the LMWH dose should be adjusted according to the membrane type and dialysis technique. This study aimed to evaluate the influence of the dialyser on anticoagulation of the extracorporeal dialysis circuit.

Methods. Thirteen patients received the same dose of LMWH through the arterial port via three dialysis techniques: high-flux haemodialysis (HF-HD), online haemodiafiltration (HDF) and expanded haemodialysis (HDx). All dialysis was performed under similar conditions: duration, 4 h; blood flow, 400 mL/min; and dialysate flow, 500 mL/min. Antifactor Xa (aXa) activity and activated partial thromboplastin time (APTT) were measured before and after the dialysis. Clotting time of the vascular access site after haemodialysis, visual clotting score of the dialyser and any complications with the extracorporeal circuit or bleeding were registered.

Results. Post-dialysis aXa activity in HF-HD (0.26 ± 0.02 U/mL) was significantly different from that in HDF (0.21 ± 0.02 U/mL, $P = 0.024$), and there was a trend in HDx (0.22 ± 0.01 U/mL, $P = 0.05$). APTT post-dialysis in HF-HD (30.5 ± 0.7 s) was significantly different from that in HDx (28.2 ± 0.64 s, $P = 0.009$) and HDF (28.8 ± 0.73 s, $P = 0.009$).

Conclusions. AXa activity in HDF was significantly lower than that in HF-HD, possibly because of more losses of LMWH through the dialyser. Given the higher anticoagulant loss in HDF and probably in HDx than in HF-HD, the enoxaparin dose administered may be adjusted according to the dialysis technique.

Keywords: anticoagulation, antifactor Xa activity, expanded haemodialysis, high-flux haemodialysis, low-molecular-weight heparin, online haemodiafiltration

INTRODUCTION

Anticoagulation of the dialysis circuit is essential to achieving optimal dialysis results. Tissue factor is activated by passage of blood through the dialysis circuit [1], which leads to the deposition of fibrin and activated platelets on the surface of the dialyser membrane and in the venous air detector chamber [2]. Therefore, most patients visiting the clinic for routine outpatient haemodialysis treatment must be prescribed anticoagulants, such as heparin, to prevent thrombin generation and premature clotting within the circuit [3].

There is no consensus on what type of heparin is most appropriate for use in dialysis [4, 5], as reflected in a study in Spain on dialysis anticoagulation: 44.1% of patients were dialysed with unfractionated heparin and 51.5% with low-molecular-weight heparin (LMWH); 4.4% received dialysis without heparin [6]. LMWHs are well tolerated and effective for haemodialysis [7–9]; however, their anticoagulant effects are difficult to monitor. Antifactor Xa (aXa) activity is the standard monitoring protocol for anticoagulant effects although it is not routinely used in clinical practice, and there is considerable debate about the end-dialysis target for aXa activity. Some reports have suggested a target of >0.4 IU/mL [10, 11], while others recommend <0.4 IU/mL [12, 13]. Because LMWHs are ~5 kDa, they are easily dialysable using high-flux membranes. In fact, reduced aXa activity has been demonstrated 4 h after administration of enoxaparin compared with low-flux membranes [14, 15].

Online haemodiafiltration (HDF) results in a higher removal rate of solutes than low- and HF haemodialysis (HF-HD) for low- and mid-sized uraemic toxins [16]. Although some studies have shown a greater need for LMWH in HDF [14], others have found no differences in the need for LMWH between HDF and HF-HD [13]. New techniques, such as expanded haemodialysis (HDx), have achieved higher capacities for the removal of medium and medium–large molecules in standard haemodialysis procedures [17, 18]. This performance is the result of the molecular weight cut-off for pore size combined with the unique internal architecture of the dialyser [19]. Although some authors recommend adapting the anticoagulant dose to the membrane surface area for medium cut-off membranes [20], there are no specific dose recommendations for anticoagulation in HDx.

The primary objective of our study was to investigate the efficacy of enoxaparin administered through the arterial port in preventing clotting in the extracorporeal circuit during HF-HD, HDx and HDF.

MATERIALS AND METHODS

Patients

This open, single-centre, prospective, cross-sectional study was conducted in the haemodialysis unit of Gregorio Marañón Hospital, Madrid, Spain. The inclusion criteria for the patients were as follows: (i) >18 years old; (ii) regular HDF sessions for 4 h on 3 days/week for at least 4 weeks; (iii) arteriovenous fistula as vascular access with blood flow >400 mL/min; (iv) stable arterial and venous pressures and recirculation <20%; (v) stable clinical conditions (defined as the absence of hospital admission within 4 weeks of the beginning of the study); and (vi) signed informed consent. The exclusion criteria were as follows: (i) history of polysulphone hypersensitivity reactions; (ii) heparin allergy; (iii) central line as vascular access; (iv) presence of residual renal function (defined as diuresis >500 mL daily); (v) anticoagulant or antiplatelet treatment; (vi) history of thrombocytopenia-induced heparin or basal thrombocytopenia (platelets <140 000/µL); (vii) pregnancy; (viii) active neoplasia; (ix) history of coagulopathy; (x) vascular access thrombosis or clotting of extracorporeal blood circuit within 3 months of the study; (xi) any disease with death foreseeable within <4 weeks; or (xii) absence of informed consent. Written informed consent was obtained from all 13 participants [12 males and 1 female; mean ± standard deviation (SD) age of 60.1 ± 4.6 years] who met the criteria, and all study procedures were conducted in accordance with the Declaration of Helsinki and its revisions.

Dialysis procedure

Patients received a standard HF-HD session using the FxCorDiax80® dialyser (Fresenius Medical Care, Bad Homburg, Germany), one HDx session using the Theranova500® dialyser (Baxter International Inc., Deerfield, IL, USA) and one online post-dilution HDF session using the FxCorDiax1000® dialyser (Fresenius Medical Care, Bad Homburg, Germany). Details of the dialyser are presented in Table 1. The dialysis sessions were conducted in the first dialysis of the week to avoid heparin interference from previous sessions in three consecutive weeks. The remaining haemodialysis sessions during the same week were prescribed according to the patient's previous treatment. A sequence of the three study sessions was randomly assigned for each patient.

The dialysers were rinsed with 2 L online solution for the FxCorDiax80® and FxCorDiax1000® systems and with 4 L of online solution for the Theranova500® system, in line with the manufacturers' instructions. For consistency, all sessions were conducted with a blood flow (Qb) of 400 mL/min, dialysis bath flow (Qd) of 500 mL/min and dialysis time of 240 min. The 14G gauge needles were used in all patients as per protocol in our centre. In addition, the HDF sessions were conducted using a volume control to reach a replacement volume of 24 L. Ultrafiltration protocols were conducted according to the needs of each patient. The total convective volume as per the EUropean DIALysis (EUDIAL) group [21] was considered as the sum of the replacement volume plus the ultrafiltration volume. During the study, each patient received a standard dose of

Table 1. Main characteristics of dialysers used in this study

Dialyzer	FxCorDiax80®	Theranova 500®	FxCorDiax 1000®
Membrane	Helixone	Polyarylethersulfone and polyvinyl-pyrrolidone blend	Helixone
Membrane surface area, m^2	1.8	2	2.3
K_{UF}, mL/h/mmHg	64	59	75
Inner diameter of hollow fibre, µm	185	180	210
Membrane thickness, µm	35	35	35
Sterilization	Steam	Steam	Steam
β2-microglobulin Sc	0.9	1	0.9

K_{UF}, ultrafiltration coefficient; Sc, sieving coefficient.

40 mg Clexane® (enoxaparin) through the arterial port 5 min after the start of dialysis. The 5008 Cordiax® system (Fresenius Medical Care) and Artis Physio® (Baxter International, Deerfield, IL, USA) system were used to monitor the HDF treatment.

Measurements and data collection

Demographic and clinical data were collected, and coagulation parameters [i.e. activated partial thromboplastin time (APTT) and aXa activity] were assessed before and after the dialysis. Pre-dialysis blood samples were drawn from the access needle immediately following needle insertion. Post-dialysis blood samples were drawn from the arterial blood line exactly 30 s after setting the blood pump at 50 mL/min to mitigate any access recirculation. To measure the APTT values and aXa activity, tests were conducted using an ACL TOP Coagulation Analyzer by HemosIL SynthASil (Instrumentation Laboratory, Bedford, MA, USA). The established reference range for APTT in the laboratory was 27–38 s, whereas that for aXa activity was 0–0.01 U/mL.

Dialyser clotting assessment

Extracorporeal thrombosis was assessed by visual inspection, scoring the extent of clotting in the filter system, the lines and bubble catcher or the dialyser, which in all cases was based on the subjective decision of the medical staff in charge of the patient. The clotting scores of the membrane and bloodlines, expansion chamber and bubble trap were determined as follows: 'Clean', no clotting of dialyser or the circuit; 'Medium', a few coloured fibres/discolouration of the circuit; 'Dirty', <50% of the visible fibres of the dialyser coloured/minimal clot in the circuit; and 'Clotted', >50% of the dialyser fibres coloured or major clot in the circuit. The manual compression time needed to stop the bleeding from the fistula was also recorded.

Any episode of haemorrhage or thrombosis during or between the dialysis sessions was registered. Major bleeding was defined as fatal bleeding, clinically overt bleeding associated with a decrease in haemoglobin concentration >2 g/dL compared with baseline, clinically overt bleeding requiring transfusion of two or more units of packed red blood cells or whole blood, or symptomatic bleeding in a critical area or organ. Minor bleeding was defined as bleeding events not meeting the above-mentioned criteria.

Statistical analyses

Data were checked for normality using the Kolmogorov–Smirnov test. Descriptive results are expressed as the means ± SDs for normally distributed continuous variables and the median and interquartile ranges for non-normally distributed continuous variables. Categorical variables are reported as percentages. Statistical comparisons were made among the three membrane types. Because of the small sample size, non-parametric tests were used. The Friedman test followed by the Wilcoxon signed-rank test for paired groups was conducted. The Holm–Bonferroni method was used to correct for multiple comparisons. Pearson's correlation coefficients were calculated to determine the correlations between continuous variables. $P < 0.05$ was considered statistically significant, and 95% confidence intervals were reported. All analyses were performed using SPSS v. 20.0, for Mac (IBM Corporation, Armonk, NY, USA).

Table 2. Baseline characteristics of the study population

General characteristics	
Sex, male, %	92
Age, years	60.1 ± 4.6
CKD aetiology, %	
Diabetes	15.4
Vascular	7.7
Glomerular	30.8
Loss of renal mass	15.4
Others	30.8
Dialysis vintage, months	54.7 ± 40.1
Dry weight, kg	71.7 ± 5.2
Laboratory parameters	
Haemoglobin, g/dL	11.1 ± 1.13
Platelets, 10^3/mcl	174.4 ± 58.1
Serum proteins levels, g/dL	6.5 ± 0.4

Data are presented as mean ± SD, or %. CKD, chronic kidney disease.

RESULTS

Thirteen patients were recruited (12 males and 1 female) with a mean ± SD age of 60.1 ± 4.6 years. All the patients had a native arteriovenous fistula. None had residual renal function (diuresis >500 mL/day). The baseline characteristics of the patients are shown in Table 2. All the patients completed the experimental sessions with all treatments with no technical problems. In particular, the regularity of the sessions was not compromised by hypotensive episodes, high transmembrane pressure or other clinical problems.

No differences were observed in the dialysis parameters (i.e. Qb, Qd, duration of sessions, size of the needles, arterial pressure, venous pressure or vascular access recirculation) among the three membrane types. APTT and aXa, compression time to stop bleeding from the fistula, and dialyser/extracorporeal circuit scores before and after the dialysis are shown in Table 3.

Post-dialysis aXa was significantly higher in HF-HD (0.26 ± 0.02) compared with HDF (0.22 ± 0.01) (P = 0.024). We found no significant trend in post-dialysis aXa in HF-HD compared with HDx (0.21 ± 0.02) (P = 0.05).

Differences were observed in K_t/V among the three dialysis types as follows: $K_t/V = 1.69 ± 0.33$ in HF-HD, 1.84 ± 0.33 in HDF and 1.82 ± 0.31 in HDx (P = 0.007). In HDF, the mean convective volume achieved was 26.4 ± 0.5 L.

There were no bleeding complications, no occurrences of blood circuit clotting and none of the filters or dialysers was scored as 'clotted'. Clotting time of the vascular access did not differ significantly among the three groups (14.2 ± 1.2 min in HF-HD, 13.9 ± 1.6 min in HDF and 17.1 ± 1.6 min in HDx). Post-dialysis aXa activity was not significantly correlated with post-dialysis APTT in HF-HD (Pearson correlation coefficient, 0.457; P = 0.11), HDF (Pearson correlation coefficient, 0.244; P = 0.44) or HDx (Pearson correlation coefficient, 0.440; P = 0.17).

DISCUSSION

We measured aXa activity to objectively evaluate the efficacy of enoxaparin in preventing coagulation with HF-HD, HDx and HDF. Although 40 mg enoxaparin was sufficient to prevent coagulation within the extracorporeal circuit with high-dialysis quality, aXa activity was significantly lower in HDF. We found no significant trend to lower post-dialysis aXa in HDx, probably because enoxaparin losses through the membrane are higher in

Table 3. Coagulation tests and clotting parameters

	HF-HD	HDx	HDF	P-value
Pre-dialysis APTT, s	27.7 ± 1.95	27.5 ± 0.6	27.7 ± 1.6	NS
Pre-dialysis aXa, U/mL	0.026 ± 0.016	0.038 ± 0.034	0.039 ± 0.008	NS
Post-dialysis APTT, s	30.5 ± 0.7	28.2 ± 0.64	28.8 ± 0.73	0.009[a] 0.009[b]
Post-dialysis aXa, U/mL	0.26 ± 0.02	0.22 ± 0.01	0.21 ± 0.02	0.024[a] 0.05[b]
Time to clotting, min	14.2 ± 1.2	17.1 ± 1.6	13.9 ± 1.6	NS
Dialyser clotting score: 'Clean', n (%)	11 (84.6)	8 (72.7)	5 (45.5)	NS
'Medium', n (%)	2 (15.4)	3 (27.3)	6 (54.5)	NS

Data are presented as mean ± SD or n (%). NS, not significant; T-Wilcoxon for paired groups with Holm correction for multiple comparisons.
[a]HF-HD versus HDF.
[b]HF-HD versus HDx.

both dialysis techniques than in HF-HD. However, our study population was small, and the power to detect differences was also limited. Currently, there is no consensus on the optimal dose of heparin in haemodialysis. According to the enoxaparin data sheet, the recommended dose is 1 mg/kg body weight (0.5 mg/kg in cases of a high risk of bleeding); however, experts initially recommended a bolus dose of 0.8 mg/kg enoxaparin because of its long half-life [22]. In our centre, we generally prescribe 0.4–0.5 mg/kg enoxaparin for intermittent haemodialysis, which has also been recommended by others, to minimize bleeding risk [1, 23]. Importantly, in our study, each patient was tested with the same dose for each dialysis type; therefore, we can exclude any bias resulting from different body weights, body mass composition, haemoglobin or plasma albumin concentrations. In addition, none of the patients had residual renal function; therefore, elimination of enoxaparin through the urine can also be excluded.

Post-dialysis APTT in HF-HD was 30.5 ± 0.7, which was significantly higher than that in HDx (28.2 ± 0.64, P = 0.009) and HDF (28.8 ± 0.73, P = 0.009). We did not find significant correlations between post-dialysis APTT and aXa levels, which was in contrast to results of previous studies [24]. Our findings are in accordance with other authors [25, 26]. These results could be explained because there are significant issues with standardization of APTTs to anti-Xa concentrations, given the variability between reagents and laboratory detection equipment used in the APTT and due to variation in Factor II [27].

Because of practical limitations, aXa activity is not generally monitored; however, determining the aXa levels allows us to assess the degree of anticoagulation [24]. Because aXa target ranges have not been validated for the prevention of extracorporeal circuit clotting, their clinical relevance and applicability are unclear. Because LMWHs are administered with the sole purpose of preventing circuit coagulation, aXa activity should be undetectable or at least below the target range, following dialysis. Some authors have suggested an aXa target range of <0.4 IU/mL [13], which is lower than the recommendations for aXa activity in the initial treatment of thrombosis (0.4–0.6 IU/mL) [28] and similar to the target for patients with an elevated risk of bleeding (i.e. 0.2–0.4 IU/mL) [2, 29]. In our study, all pre-dialysis aXa activity levels were below the anticoagulation dose limit, which indicated no previous heparin interference. Post-dialysis aXa values were 0.26 ± 0.02 in HF-HD, 0.21 ± 0.02 in HDF and 0.22 ± 0.01 in HDx. These findings are similar to those of other studies [29] and conform to the standards for thrombosis avoidance. There were significant differences in post-dialysis aXa activity between HF-HD and HDF (0.26 ± 0.02 versus

0.21 ± 0.02, respectively; P = 0.024), which was most likely the result of enoxaparin removal during HDF, as has been previously described [14].

To our knowledge, no studies have compared the proper anticoagulant dose in HDx with other membrane types. Some authors have recommended an anticoagulant dose that is the same as that for another membrane with the same surface [20]; however, in this study, we observed a trend to higher aXa values in HF-HD compared with HDx (0.26 ± 0.02 versus 0.22 ± 0.01, respectively; P = 0.05). Because HDx removes a substantial number of mid-size molecules, we postulate that these differences stem primarily from losses of enoxaparin through the membrane. We did not find differences in post-dialysis aXa activity between HDF and HDx, most likely because both achieve similar clearance of mid-size molecules. In addition, the composition of the membrane could play a role in LMWH anticoagulant activity [4, 14]; however, we were not able to test this because of our small sample size. For all these reasons, we believe that the LMWH dose should be adjusted to the membrane surface and should take into account the type of haemodialysis (HF-HD, medium cut-off or online HDF).

We found no significant trend towards poorer clotting scores in the dialyser and extracorporeal circuit with HDx and HDF. At the end of the session, 84.6% of patients with HF-HD, 72.7% with HDx and 45.5% with HDF had a clotting score within the 'Clean' range. Previously, higher levels of thrombin generation and worse visual clotting scores have been observed when anti-Xa levels were <0.3 IU/mL at the end of post-dilution haemodiafiltration [30]. However, in our study, we met the accepted standards of dialysis quality as the mean K_t/V was 1.69 ± 0.33 in HF-HD, 1.84 ± 0.33 in HDF and 1.82 ± 0.31 in HDx, and the mean convective volume in HDF was 26.4 ± 0.5 L. In addition, all dialysis sessions were conducted without any technical problems, pressure alarms or clotting events, probably due to enoxaparin effect and the high blood flow achieved. There were no bleeding complications. Patients at high risk of bleeding were excluded and only one session in each arm of treatment was conducted, so more studies are needed in this regard. Bleeding time is clinically longer in HDF despite lower aXa. However, it is not statistically significant so it could be related to intraindividual variability. Additional studies are needed to assess whether increasing the LMWH dose would reduce thrombosis within the dialyser/extracorporeal circuit with increased depurative efficacy and without a higher risk of bleeding.

Experts advise heparin administration at the inlet line [1, 3, 22, 30, 31]. However, in some guidelines [32] and in the enoxaparin data sheet, administration via the arterial line is

recommended, whereas no recommendation concerning the administration site is provided in other guidelines [5, 33–35]. Most studies have either indicated that LMWHs are injected at the inlet line [7, 36, 37] or have not specified the administration site; therefore, we used the arterial port in our study.

Several limitations of our study must be acknowledged. First, our sample size was small, which limited the statistical power to detect differences. Secondly, this was a short-term study with a single treatment arm and was not designed to provide information on long-term safety for flexible enoxaparin dosing. Thirdly, intra-individual variability was not evaluated. In addition, we excluded some patients who displayed an elevated risk of bleeding, including those on anticoagulants or antiplatelet agents; therefore, our study could not predict complications of long-term enoxaparin use through the arterial port.

Thus, 40-mg enoxaparin administered through the arterial port was sufficient to prevent coagulation within the extracorporeal circuit; however, additional studies are needed to compare arterial with venous port administration because it is plausible that venous port administration decreases LMWH losses through the dialyser, leading to a lower required dose and/or improved clotting scores, particularly in HDF and HDx. In our study, we did not observe any haemorrhagic complications although long-term follow-up is needed with this patient population.

CONCLUSIONS

The results of our study indicated that 40-mg enoxaparin administered through the arterial port was sufficient to prevent coagulation within the extracorporeal circuit with high-dialysis quality; however, aXa activity was significantly lower in HDF, most likely because of the greater LMWH losses through the dialyser.

We found no significant trend to lower aXa in HDx, probably due to high LMWH losses through the membrane. Thus, the dose of enoxaparin administered through the arterial port should be adjusted to the membrane type and size, and dialysis technique should be taken into account.

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AUTHORS' CONTRIBUTIONS

A.S. contributed to design, statistical support and drafted the article. N.M. contributed importantly to conception, design and statistical support. A.V. contributed to conception and provided intellectual content of critical importance. C.P. performed all the coagulation tests. T.L., I.A. and L.C. contributed to data collection. S.A., M.G. and J.M.L.-G. revised the article.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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