KI REPORTS
KIReports.org
CLINICAL RESEARCH

Arterial Versus Venous Port Site Administration of Nadroparin for Preventing Thrombosis of Extracorporeal Blood Circuits in Patients Receiving Hemodiafiltration Treatment

Hedia Hebibi[1,2], David Attaf[3,6], Laure Cornillac[3,6], Jejiga Achiche[2], Fatia El Boundri[3], Patrick Francais[1], Charles Chazot[3] and Bernard Canaud[4,5]

[1]NephroCare Île-de-France, Villejuif, France; [2]NephroCare Île-de-France, Bièvres, France; [3]Fresenius Medical Care, Ile de France, France; [4]Global Medical Office, Fresenius Medical Care Deutschland, Bad Homburg, German; and [5]Montpellier University, Montpellier, France

Introduction: Administration of low-molecular-weight heparins (LMWHs) is necessary for preventing extracorporeal circuit thrombosis during hemodialysis. A substantial amount of LMWH is removed with online hemodiafiltration (OL-HDF) when administered through the inlet site of the extracorporeal circuit. Consequently, administration of LMWH at the outlet site appears to be more efficient. In this study we aimed to compare the effects of nadroparin calcium (NAD) administered through the outlet versus the inlet port site in postdilution OL-HDF and assess the NAD dose reduction.

Methods: Forty-nine hemodialysis patients were included in 3 consecutive 6-week studies as follows: phase I, inlet port line; phase II, outlet port line; and phase III, outlet port line with reduced dose. We evaluated clotting in the hemodialyzer and venous bubble trap, the dialysis dose (*Kt/V*), and substitution volume.

Results: Thirty four percent, 63%, and 66% were categorized as "white" during phases I, II, and III, respectively. During phases I, II, and III, 75%, 93%, and 95% of the venous bubble traps were "clean," and 9%, 0.6%, and 0.4% of the dialyzers clotted, respectively. Average NAD dose was 0.43 ml during phase I and 0.3 ml during phase II. During phase III, the LMWH dose was reduced by 33% to 50% in 15 patients. In phase III, *Kt/V* improved from 1.64 to 1.75 and substitution volume increased from 20.18 to 21.96 L.

Conclusions: When using OL-HDF, a single administration of NAD at the outlet port line allows for a significant dose reduction and was associated with improved dialysis performance.

Kidney Int Rep (2021) **6,** 351–356; https://doi.org/10.1016/j.ekir.2020.11.020
KEYWORDS: low-molecular-weight heparin; nadroparin; postdilution hemodiafiltration

Prevention of extracorporeal circuit thrombosis during hemodialysis and hemodiafiltration (HDF) therapy is necessary to facilitate treatment. Due to their good safety profile and easier handling, low-molecular-weight heparins (LMWHs) have been increasingly used in recent decades.[1–5] The longer half-life of LMWHs allows for use of a single i.v. bolus dose at the start of the dialysis session for the conventional 4 hours, without the need for additional coagulation testing or monitoring.[1,2]

The safety and efficacy of LMHWs in hemodialysis have been largely proven over time, based on extensive clinical experience.[1,6,7] Occasionally, LMWH use may be associated with oozing at the needle puncture or may require a prolonged compression time for vascular access. This side effect is likely a result of accumulation of the agent, which can be overcome either by reducing the dose or spacing injections. However, in the absence of adequate anticoagulation, a premature interruption of the dialysis session may occur due to partial or complete thrombosis of the extracorporeal circuit.

Adequate prevention of extracorporeal circuit thrombosis in HDF remains a clinical challenge that reflects a delicate balance between clotting and bleeding. An additional issue with LMWHs in dialysis is that their relatively low molecular weight that

Correspondence: Hedia Hebibi, NephroCare Villejuif hemodialysis center, 1 Mail du professeur Georges Mathé, Villejuif 94800, France. E-mail: had.hebibi@gmail.com

[6]DA and LC contributed equally to this work.

Received 22 September 2020; revised 10 November 2020; accepted 17 November 2020; published online 31 December 2020

can lead to them being cleared. Interestingly, the very efficacy of LMWHs depends on several factors: its clearance, which is a function of the agent; the administration port site; the dialysis modality, such as high-flux dialysis and online HDF (OL-HDF); and pharmacokinetics/pharmacodynamics of the agent (i.e., anti-Xa binding membrane capacity). The molecular weight of LMWHs is between 3600 and 6500 Da.[8] A substantial amount of LMWHs are removed during OL-HDF and high-flux dialysis when administered in the inlet port line of the extracorporeal circuit.[8] It has been shown that LMWH dosing tends to be 10% to 25% higher during postdilution OL-HDF compared with high-flux dialysis.[8] Based on these findings, administration of LMWHs at the outlet port site of the extracorporeal circuit has been proposed.[8]

In this study, we aimed to compare the effects of nadroparin administered either through the outlet (new procedure) or inlet (old procedure) port site of the extracorporeal blood circuit in postdilution OL-HD. We also explored the possibility of nadroparin calcium (NAD) dose reduction, based on its use during outlet port site injection (new procedure).

METHODS

Patients

In this study we enrolled 49 stage 5 chronic kidney disease patients from among 60 patients on maintenance therapy with HDF treated at 2 dialysis facilities of Île-de-France (Supplementary Figure S1). All patients agreeing to participate in these procedures received adequate information about the protocol and signed a consent form.

This prospective study was conducted in a quality improvement care practice over a period of 18 weeks from February 1 to June 16, 2018. Patients on vitamin K antagonists were excluded from this study. NAD (Fraxiparine; Aspen Pharmaceutical Corp, Rueil Malmaison, ile de France, France) was routinely used. NAD was administered at the inlet port of the extracorporeal blood line at the start of the dialysis sessions.

Maintenance doses of NAD (1900–5700 IU) per patient were established clinically based on extracorporeal circuit appearance, the absence of both visible clotting within hemodialyzer fibers and prolonged bleeding, and access compression time after dialysis. Ten patients received antiplatelet therapy, either aspirin ($n = 4$) and/or clopidogrel ($n = 6$), for cardiovascular comorbidities.

Study Design

The flowchart of this study is presented in Supplementary Figure S1. The protocol consisted of 3 phases of 6 weeks each. During phase I, NAD was administered as an i.v. bolus at the start of the HDF session at the inlet port of the extracorporeal circuit upstream the hemodialyzer. During phases II and III, NAD was administered as an i.v. bolus at the outlet port of the extracorporeal circuit downstream the hemodialyzer. The NAD administration switch (from inlet to outlet port site) within the extracorporeal circuit was assigned to all patients during phases I and II, with the same NAD dosing throughout 12 weeks.

Hemodialyzer and venous bubble trap chamber clots were assessed using a semiquantitative visual scale as shown in Supplementary Figure S2A and B. Blood was sampled from the vascular access at the start of the hemodialysis session before nadroparin administration.

Primary endpoints were visual clotting scales at the end of the session. Secondary endpoints were loss of extracorporeal circuit, bleeding time, NAD dose, the dialysis dose (Kt/V), transmembrane pressure, and substitution volume. The pressure measurements along the circuit were logged. The titration of the NAD dose during a 6-week phase was performed to reach anti-Xa activity <0.3 IU/ml.

Hemodiafiltration

Postdilution HDF treatment was performed using a dialysis machine (Model 5008; Fresenius Medical Care, Bad Homburg, Germany). The AutoSub Plus mode was activated in all cases to ensure fully automated reinjection of substitution volume. The AutoFlow mode was also activated to ensure precise matching of dialysate flow to blood flow.

High-flux hemodialyzers with different effective surface areas were used, including the FX CorDiax 1000 (2–3 m^2), FX CorDiax 800 (2 m^2), and FX CorDiax 600 (1.6 m^2) (all from Fresenius Medical Care, Bad Homburg, Germany), and the BG-2.1 (2.1 m^2) (Toray Medical, Urayasu, Japan). Hemodialyzer priming was ensured with the online function of the machine being fed with ultrapure dialysis fluid without heparin. During phases I and II, the maintenance NAD dose given before the study was used. HDF sessions lasted 240 minutes with a mean effective blood flow of 350 ml/min and a substitution flow of 75 ml/min.

The ultrafiltration rate required for correcting fluid overload was added to this substitution flow. No i.v. medication was administered during the HDF sessions. At the end of the session, the extracorporeal blood circuit was rinsed back using the automated online rinsing program with 300 ml of ultrapure dialysis fluid.

Sample Collection

Demographic and clinical data were collected and coagulation parameters (anti-Xa activity) were assessed

before and after the dialysis session. Predialysis blood samples were drawn from the vascular access site immediately after needle insertion. Postdialysis blood samples were drawn from the arterial blood line 3 minutes after reducing blood pump speed to 50 ml/min to mitigate access recirculation.

Blood samples were collected in citrated tubes (Venosafe 3.6 ml, 0.109 mol/L buffered sodium citrate; Terumo Europe, Leuven, Belgium) for measurement of anti-Xa, in tubes with gel and the clotting activator (Venosafe Autosep; Terumo) for C-reactive protein (CRP) and urea in potassium–ethylenediamine tetraacetic acid tubes (BD, Plymouth, UK) for hemoglobin. During phase III, the NAD dose was reduced stepwise to achieve the targeted safe and efficient anti-Xa activity.

Hemodialyzer Clotting Assessment

During the 3 phases, extracorporeal thrombosis was assessed by visual inspection, scaling, and scoring the extent of the clot within the hemodialyzer (fibers, bundle, and head), tubing lines and venous bubble trap. In all cases this assessment was based on subjective visual analysis by the medical staff in charge of the patient. The clot scoring of the hemodialyzer, tubing line and bubble trap were characterized as follows: "white or clean" = white color of fibers and no visible clot within the filter or blood line; "light pink" = a few dark red fibers; "substantial clot" = <50% of dark red fibers within the dialyzer and/or minimal clot within the blood line; and "major clot" = >50% of dark red fibers within the dialyzer or massive clot within the dialyzer and/or blood line.

Clot scaling and scoring of the dialyzer and blood circuit included clotting score for the dialyzers and visual scale (Supplementary Figure S2A) and clotting score for blood line and venous bubble trap (Supplementary Figure S2B). The manual compression time of vascular access needed to stop oozing from needling sites was also recorded.

Analytical Techniques

Anti-Xa activity was measured using a chromogenic method (Biophen Heparin; Hyphen BioMed, Neuville-sur-Oise, France) on an STA-C device (Diagnostica Stago, Asnières, France) with a detection limit of 0.05 IU/ml.

Statistical Analysis

Statistical analysis was performed using the Wilcoxon matched pairs signed rank test, as appropriate for a repeated-measures design where the same subjects are evaluated under 2 different conditions. This is the nonparametric equivalent of the parametric paired t test. Data are expressed as mean ± SD. Comparisons between groups were performed using nonparametric test analysis. $P < 0.05$ was considered statistically significant.

RESULTS

This prospective bicentric study was conducted in 49 hemodialysis patients in a quality improvement care practice. The mean age of participants was 66 (range 26–92) years. Twenty-nine patients were male, 42 had a native arteriovenous fistula, and 7 had a central venous catheter. The median body weight of the patients was 69 (52–110) kg (Supplementary Table S1). Twenty patients were diabetic and obese. Ten patients received antiplatelet therapy, either aspirin (n = 4) and/or clopidogrel (n = 6), for cardiovascular comorbidities.

During phase I (inlet), 882 HDF sessions were performed. As indicated, NAD was administered within the inlet port site (arterial). The mean substitution volume achieved was 22.7 (20.5–23.2) L. During phase II (outlet), 810 dialysis sessions were performed on 45 patients (41 arteriovenous fistula and 4 central venous catheter) of the initial cohort. Four patients withdrew from the study due to transfer to another center or transplant. NAD was administered at the outlet port site. The mean substitution volume achieved in phase III was 21 (20.5–23.3) L. Thirty-five patients (32 arteriovenous fistula and 3 central venous catheter) continued in the study for 6 additional weeks and received NAD at the outlet port site at a reduced dose. During phase III, 630 sessions were performed, with a reduction of the NAD dose (Supplementary Table S1). During this phase, NAD was titrated individually to reach a target of ≤0.3 IU/ml of anti-Xa activity.

Visual Clotting Scores (Dialyzer, Bubble Trap) and Circuit Loss

Interestingly, upon transitioning from phase I to phase II, namely from inlet to outlet port site, with the same NAD dose, the clotting score was reduced (cleaner) and the visual score for the hemodialyzers and blood circuit improved from 37% to 63% (Supplementary Figure S3).

Major clotting of the hemodialyzer and blood circuit occurred in 9% of patients during phase I inlet administration as compared with 1% during phase II outlet administration. The presence of a white or clean appearance of the bubble trap increased from 72% to 92% during the outlet site administration phase (+20%).

During phase III, the percentage of white and clean dialyzers was 67%, compared with 63% in phase II. No bleeding or thrombosis episodes were observed during or between dialysis sessions within the study period. Mean bleeding time did not change between the 2 phases. Furthermore, 8 losses of extracorporeal circuit

were observed during phase I as compared with none in phases II and III (outlet site with NAD dose reduction).

Coagulation Parameters

The mean bleeding time did not change during the three 6-week periods.

Hemodialyzer Type and Clotting

The large-surface FX CorDiax 1000 dialyzers had higher clotting scores in phase I (inlet site) when compared with phase II (outlet site) (45 vs. 24 dialyzers). No difference was observed with smaller surface area membranes (FX CorDiax 800 and 600 devices).

Combined NAD Administration via Outlet Port Site With Dose Reduction

During phase III, NAD dose was reduced by half in 9 patients, by one third in 6 patients, and remained unchanged in 19 patients. Percent of dialyzer clotting score remained identical to that in phase II.

Parameters Related to Dialysis Adequacy

The switch from inlet to outlet site NAD administration was associated with an improvement in Kt/V from 1.64 to 2.01 ($P < 0.05$), a decrease in venous pressure from 171.78 to 167.02 ($P < 0.05$) mmHg, and an increase of substitution volume from 20.18 L to 21.96 L ($P < 0.05$) (Supplementary Table S1).

DISCUSSION

Two recent randomized, prospective studies have shown that outlet administration of LMWHs has been beneficial for the prevention of extracorporeal circuit thrombosis in patients receiving high-flux hemodialysis and HDF, with a substantial dose reduction of the antithrombotic agent.[8–10] LMWHs are not generic compounds; each one has its own pharmacokinetic and pharmacodynamic specificity with certain conditions of use and differing levels of efficiency. Seeing that no study had done so before, it became our aim to perform this procedure with specific use of NAD, a commonly used antithrombotic agent for hemodialysis in France.

Our study was designed to lead to improved care practices for dialysis patients and for optimizing the use of NAD in OL-HDF. Accordingly, we used a stepwise approach to assess 2 options for preventing extracorporeal circuit thrombosis by relying on single-dose administration of NAD at the start of an OL-HDF session. The first step consisted of changing the port site and switching from the arterial line (inlet port site) to the venous line (outlet port site) while keeping the same NAD dose (phases I and II). The second step consisted of reducing NAD dose due to the novel use of the outlet port site for injection while probing individual response and adjusting NAD dose to a targeted anti-Xa activity (≤0.3 IU/ml). NAD is an LMWH prepared from porcine heparin by nitrous acid depolymerization. NAD has a mean molecular weight of 4.5 (range 1–10) kDa and is less polydisperse than unfractionated heparin, with 50% of the molecules having a molecular weight of 4 to 5.5 kDa.[11] Also, NAD is currently used in routine clinical dialysis due to its favorable efficiency and safety profile.[12,13] OL-HDF is recognized as the most efficient renal replacement modality in terms of solute removal capacities through its ability to tackle accumulation of uremic toxins with middle and large molecular weights up to 15 to 20 kDa.[14] Based on previous studies and considering its molecular weight, it is apparent that administration of a single dose of NAD at initiation of OL-HDF at the inlet port site (arterial line), as recommended by the instruction leaflet provided by the pharmaceutical manufacturer, risks clearing up to one third of the NAD dose within the first HDF passage, thus wasting a substantial amount of active product and increasing the risk of extracorporeal thrombosis.

Our findings indicate that the switch from inlet port site (old procedure) to outlet port line (new procedure) administration of NAD resulted in a significant improvement in visual clotting scores for dialyzers and tubing lines in OL-HDF. Furthermore, outlet port site administration permitted a significant NAD dose reduction. As indicated previously, titration targeting a safe and efficient anti-Xa activity (anti-Xa ≤0.3 IU/ml) was achieved in the majority of patients with significantly lower NAD doses. It is also of interest to highlight the fact that, in all cases, NAD was administered as a single-dose bolus injection at the start of treatment without any additional dose administration within the course of the HDF sessions.

The interpretation of these findings is easy and tends to confirm results of previous studies performed with various LMWH agents, indicating a substantial loss of the active agent in high-flux hemodialysis and HDF.

When NAD is administered at the inlet port site (old procedure) with a single dose at the initiation of hemodialysis, one can estimate an initial loss of dose of up to 30% during the first pass, which confirms recent findings by Dhont *et al*.[8] Initial loss tends to be greater with high-efficiency HDF. In addition, by adopting this route, NAD dose may be further reduced and customized to the patient's needs while targeting safe and efficient anti-Xa activity, as shown in phase III of our study.

Dialysis modality (i.e., low flux, high flux, HDF) and efficiency should be considered when choosing the route of administration and dose of LMWHs in

patients receiving extracorporeal treatment. For example, in a similar study performed in patients receiving hemodialysis with low-flux dialyzers, Vanuytsel *et al.*[15] compared safety and efficacy of NAD administered via different routes. They found that the same dose of NAD, administered within the venous line after priming the extracorporeal circuit with a fraction of the total dose administered, was similar in terms of anti-Xa blood activity levels to the one administered via the arterial line.[15] Such a difference may be easily explained by treatment conditions, including membrane permeability and dialysis performances. When compared with low-flux dialyzers, high-flux dialyzers allow clearance and removal of larger compounds, leading to a significant loss of nadroparin when administered through the arterial line.[9,14,15]

Due to the increasined use of high-flux hemodialyzers and HDF, the effect of LMWH administration route has become a subject of concern and several clinical studies have been undertaken. Interestingly, 2 of the most recent studies of high scientific value had similar conclusions and advised administration of LMWHs at the outlet port site or the venous line and not at the inlet port site. In a randomized, crossover study by Kurtkoti *et al.*[9] involving 16 (8 hemodialysis and 8 HDF) patients, venous line administration of enoxaparin achieved greater 4-hour blood anti-Xa activity when compared with arterial line administration with an equivalent dose. Based on this finding, the authors suggested a 25% or 50% reduction in dose of venous line enoxaparin, as compared with the dose administered through the arterial line in patients receiving either hemodialysis or HDF. In the randomized, crossover trial by Dhondt *et al.*,[8] involving 13 patients receiving HDF, injection of tinzaparin at the inlet line before the start of the session was associated with a loss of anticoagulant activity ($\approx$30%) and was therefore not recommended. In addition, they found that outlet administration kept anti-Xa activity >0.3 IU/ml at the end of the session, a condition associated with less clotting and improved dialysis efficiency.

Despite clinical advantages associated with outlet port site administration in hemodialysis, clinical practice surveys have tended to show that this option is rarely applied.[4] In most studies, LMWHs are injected at the inlet port site or arterial line,[4,8,10,16] or an even worse administration site not mentioned.[8] As is usual in medicine, this observation gives further credence to the fact, there is still a gap between the best clinical practices and the manufacturer's instruction for use. For example, in the manufacturer's leaflet of tinzaparin, enoxaparin, and nadroparin, administration of these agents via arterial line (inlet port site) is still recommended, whereas, in best clinical practice guidelines, no recommendation regarding administration sites is mentioned.[17]

In view of these findings we strongly advise manufacturers, medical agencies, and health regulatory authorities to come together and propose to revise the recommendations for LMWH administration in high-flux dialysis and HDF by switching from inlet to outlet port site administration with a single bolus dose at the initiation of the session.

This recommendation would hold true for relatively short treatment sessions (<4 hours), but the problem is different with daily (repetitive treatment) or long nocturnal treatment (multiple dose injections). In such cases, a risk of LMWH accumulation exists in chronic kidney disease patients and therefore dose adjustment and anti-Xa activity monitoring would be strongly suggested.[12,18,19]

The intent of our study was to suggest improvements in clinical practice in dialysis and optimization of the use of NAD in patients receiving HDF. Overall, our findings are in agreement with recent randomized, crossover studies. We acknowledge some limitations to our study: first, it was not a randomized, crossover trial, meaning that we had no control group or randomization order; second, anti-Xa blood activity levels were measured only once during each phase of the study; and third, health-related costs/benefits were not calculated, but it is obvious that a NAD dose reduction of up to 50% would significantly impact cost. Despite these limitations, our study has the advantages of having been conducted at 2 centers and with a relatively large number of patients in a real-life practice—2 conditions that would tend to increase reliability and generalizability of the results. Moreover, we could clearly demonstrate the differences in visual blood scores of arterial versus venous line administration of NAD.

Switching from inlet to outlet port site administration of NAD in OL-HDF is an easy change to make in clinical practice and it has positive effects. It reduces the clotting risk of both the dialyzer and tubing, improves clinical performance in both diffusive and convective clearances, and reduces NAD dose consumption by up to 25%, with a likely cost reduction.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The authors thank the dialysis nursing teams of NephroCare Villejuif and NephroCare Bievres.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Study flowchart. Three study phases with different routes of administration (arterial and venous low-molecular-weight heparin: nadroparin).

Figure S2. (A) Evaluation of the dialyzer status. Semiquantitative visual scale for evaluation of the dialyzer status in each hemodialysis session. (B) Evaluation of venous drip chamber status. A semiquantitative visual scale was used to evaluate venous drip chamber status in each hemodialysis session.

Figure S3. Evaluation of dialyzer and venous drip chamber status for each treatment period, according to the nadroparin site administration (phase 1: inlet port line; phase 2: outlet port line; phase 3: outlet port line with nadroparin dose reduction).

Table S1. Treatment conditions.

REFERENCES

1. Barradell LB, Buckley MM. Nadroparin calcium. A review of its pharmacology and clinical applications in the prevention and treatment of thromboembolic disorders. *Drugs*. 1992;44:858–888.
2. Janssen MJ, Huijgens PC, Bouman AA, et al. Citrate versus heparin anticoagulation in chronic haemodialysis patients. *Nephrol Dial Transplant*. 1993;8:1228–1233.
3. Lazrak HH, René E, Elftouh N, Leblanc M, Lafrance JP. Safety of low-molecular-weight heparin compared to unfractionated heparin in hemodialysis: a systematic review and meta-analysis. *BMC Nephrol*. 2017;18:187.
4. Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. *J Am Soc Nephrol*. 2004;15:3192–3206.
5. Wong SS, Lau WY, Chan PK, Wan CK, Cheng YL. Low-molecular weight heparin infusion as anticoagulation for haemodialysis. *Clin Kidney J*. 2016;9:630–663.
6. Stöbe J, Siegemund A, Achenbach H, Preiss C, Preiss R. Evaluation of the pharmacokinetics of dalteparin in patients with renal insufficiency. *Int J Clin Pharmacol Ther*. 2006;44:455–465.
7. Guillet B, Simon N, Sampol JJ, et al. Pharmacokinetics of the low molecular weight heparin enoxaparin during 48 h after bolus administration as an anticoagulant in hemodialysis. *Nephrol Dial Transplant*. 2003;18:2348–2353.
8. Dhondt A, Pauwels R, Devreese K, Eloot S, Glorieux G, Vanholder R. Where and when to inject low molecular weight heparin in hemodiafiltration? A cross over randomised trial. *PLoS One*. 2015;10(6).
9. Kurtkoti J, Bose B, Hiremagalur B, Sun J, Cochrane T. Arterial line versus venous line administration of low molecular weight heparin, enoxaparin for prevention of thrombosis in the extracorporeal blood circuit of patients on haemodialysis or haemodiafiltration: a randomized cross-over trial. *Nephrology (Carlton)*. 2016;21:663–668.
10. Davenport A. Low-molecular-weight heparin for routine hemodialysis. *Hemodialysis Int*. 2008;12:S34–S37.
11. Davis R, Faulds D. Nadroparin calcium. A review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. *Drugs Aging*. 1997;10:299–322.
12. Buitenwerf E, Risselada AJ, van Roon EN, Veeger NJ, Hemmelder MH. Effect of nadroparin on anti-Xa activity during nocturnal hemodialysis. *BBA Clin*. 2015;3:276–279.
13. Russcher M, Josephus Jitta N, Kraaijenhagen RJ, Fijnheer R, Pasker-de Jong PC, Gaillard CA. Preemptive dosage reduction of nadroparin in patients with renal failure: a retrospective case series. *Clin Kidney J*. 2013;6:473–477.
14. Locatelli F, Canaud B. Dialysis adequacy today: a European perspective. *Nephrol Dial Transplant*. 2012;27:3043–3048.
15. Vanuytsel JL, Lins RL, Zachée P, et al. Comparison of different routes of administration of nadroparin in hemodialysis. *Clin Nephrol*. 1999;52:322–325.
16. Davenport A. Low-molecular-weight heparin as an alternative anticoagulant to unfractionated heparin for routine outpatient haemodialysis treatments. *Nephrology (Carlton)*. 2009;14:455–461.
17. European Best Practice Guidelines Expert Group on Hemodialysis European Renal Association. Section V. Chronic intermittent hemodialysis and prevention of clotting in the extracorporeal system. *Nephrol Dial Transplant*. 2002;17.
18. Davenport A. Low-molecular-weight heparin for routine hemodialysis. *Hemodialysis Int*. 2008;12(suppl 2):S34–S37.
19. Chuang FR, Chen TC, Lee CH, et al. Clinical safety and anticoagulation efficacy of low-molecular-weight heparins in chronic hemodialysis patients: a single medical center experience. *Renal Fail*. 2011;33:990–997.