Renal Failure, 33(10): 990–997, (2011)

ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2011.618905

informa
healthcare

CLINICAL STUDY

Clinical Safety and Anticoagulation Efficacy of Low-Molecular-Weight Heparins in Chronic Hemodialysis Patients: A Single Medical Center Experience

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Abstract

Background: In many countries low-molecular-weight heparins (LMWHs) are increasingly used for hemodialysis (HD). Low-range activated clotting time (ACT-LR) values and anti-Xa activity had been used to monitor the degree of anticoagulation caused by LMWH. However, the facilities are not easily available at most hospitals. Such data are limited in Taiwan. *Methods*: A total of 76 patients receiving maintenance HD were prospectively enrolled. The HD patients were randomized to receive either nadroparin or enoxaparin and checked the ACT-LR values and anti-Xa activity. We aimed to analyze ACT-LR values and anti-Xa activity along with the clotting of the dialyzer or bleeding events associated with two LMWHs after they were administered. We also aimed to determine the dose necessary to reach maximum safety and efficacy. *Results*: We found no significant differences in LMWH dosage, ACT-LR values, and anti-Xa activity between the two groups. There were no significant differences in bleeding/adverse events and extracorporeal circuit thrombosis between the two groups. Most of the bleeding and adverse events were subcutaneous minor bleeding. No major bleeding or mortality was found. We found significant differences in mean dosage, cost, bleeding/adverse effect, and extracorporeal circuit thrombosis between excessive and reduced nadroparin dosage groups. *Conclusion*: LMWH is not still routinely used due to its high cost in Taiwan. In our clinical experience, nadroparin and enoxaparin exhibited high levels of safety and efficacy in chronic HD patients. Reduced LMWHs dosage could promote patient's safety and decreased HD cost in HD patients with excessive dosage of LMWHs.

Keywords: low-molecular-weight heparin, hemodialysis, low-range activated clotting time, anti-Xa activity

INTRODUCTION

In many countries, low-molecular-weight heparins (LMWHs) have replaced unfractionated heparin in various clinical applications including the treatment of thrombosis and as anticoagulants in hemodialysis (HD).[1–7] Other advantages include low incidence rates of heparin-induced bleeding,[8] osteoporosis,[9] thrombocytopenia,[10] and lipid abnormalities.[11]

LMWHs are increasingly being used in the current practice of HD. Several LMWHs are now available,[7] but only previous some investigations have compared LMWH to unfractionated heparin in term of their efficacy and safety profiles in chronic HD patients.[3,6,12,13] Few studies have directly compared two commonly used LMWHs in chronic HD patients.[14–16]

Low-range activated clotting time (ACT-LR) (in seconds) and anti-Xa level have been used to monitor the

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Received 14 May 2011; Revised 21 July 2011; Accepted 12 August 2011

degree of anticoagulation of LMWHs.[7,17,18] However, the facility for measuring ACT-LR or anti-Xa level is not easily available at most hospitals. Although several LMWHs have been widely used for many years, there are no reliable data to guide the interpretation of ACT-LR or anti-Xa levels. Accurate interpretations are necessary in order to monitor or properly adjust LMWH dosage. Most of these studies involve a small sample size and were performed primarily in Western countries. Such data are quite limited in Taiwan. Different LMWHs have different pharmacokinetic and pharmacodynamic profiles.[19–21] LMWH dosage is usually adjusted on the basis of clotting of the dialyzer or the occurrence of bleeding/adverse event. LMWH may also be adjusted to individual needs. Bleeding events are a major concern.

MATERIALS AND METHODS

A total of 76 patients receiving maintenance HD were enrolled in our study. The HD patients were randomized to receive either nadroparin or enoxaparin. We determined the ACT-LR and anti-Xa levels from 1 July 2009 to 31 December 2009 for 76 chronic HD patients. We also checked 24 healthy subjects' ACT-LR for baseline data simultaneously. Exclusion criteria were HD duration less than 1 year, underling bleeding disorders, receiving anticoagulant therapy, or antiplatelet agent therapy. All study subjects provided written informed consent and the ethical committee approved this study protocol. Patient characteristics (age, sex, body weight, drug use, blood pressure, and volume status) were recorded.

The prescription of regular HD patients was three sessions per week for 3–4 h per session and an average blood flow rate of 250 mL/min to achieve the optimal target prescription of 1.4 Kt/V. HD durations must be adjusted to the tolerance of ultrafiltration in order to reach the dry weight. All sessions use the traditional regimen of bicarbonate dialysate buffer. The types of biocompatible membranes were around 80%, major including polysulfone. Approximately 10% of the patients had synthetic graft and 90% had native fistula.

For both groups of patients, optimization of LMWH dosage was required for each individual patient and was determined by taking into account the technical conditions of the dialysis. The excessive LMWH dosage represented ACT-LR exceeding 2.5-fold with or without clinically occurred bleed. Blood samples were collected in order to determine ACT-LR and anti-Xa levels before HD, after 1, 2, and 3 h, and at the end of HD. In addition, we checked the patient's anti-Xa level in order to determine if a correlation existed with those who suffered from clotting of the dialyzer or a bleeding event.

Overall safety of the LMWHs used in our study was assessed by noting all minor and major bleeding. Major bleeding was defined as any clinically overt bleeding that required hospitalization or transfusion, bleeding into a critical organ or space, or bleeding that resulted in death. Any other bleeding was classified as minor. Minor bleeding events included occurrences such as subcutaneous bleed, subconjunctival hemorrhage, bleeding at vascular access sites, and hemorrhoid bleeding. In order to determine overall the efficacy of the LMWHs, the dialyzer was scored similarly using the following ratings: 1 = good, clear dialyzer; 2 = medium, pink dialyzer; 3 = poor, partly clotted dialyzer; and 4 = total clotting of the dialyzer requiring a change of the extracorporeal circuit. The lines and the bubble catcher were observed and were graded at the end of each dialysis procedure based on the following ratings: 1 = no clots; 2 = minimal clots; 3 = moderate clots; and 4 = severe clots. To determine the efficacy of the LMWH, we checked dialyzer clot and the lines/the bubble catcher from each dialysis procedure. We recorded clotting of the dialyzer or the lines/the bubble catcher and occurrence of bleeding/adverse events for a period of 1 year for each patient.

We measured ACT-LR and anti-Xa levels after a single dose injection of LMWH in order to assess the pharmacokinetic characters. The aim of this study was to further clarify the relationship between bleeding risks and ACT-LR or anti-Xa level in patients using two LMWHs for HD and to study the clinical safety and anticoagulation efficacy of LMWHs.

Laboratory Testing

The HEMONOX test uses a proprietary lapidated recombinant rabbit brain tissue factor (Pel-Freez Corp, Rogers, AR, USA) based reagent and formulation buffer, which has been optimized to measure the anticoagulation effect of LMWH within a disposable cuvette. The HEMOCHRON® Jr. ACT-LR test uses a Celite activator due to its excellent heparin sensitivity and reflects the activity of factor Xa in generating thrombin and leading to the formation of a fibrin clot. The test demonstrates linearity at heparin concentrations up to 2.5 units of heparin per milliliter of blood. The HEMONOX assay was performed using the HEMOCHRON® Jr. Signature+ (software version 2.4 or higher, Olsen Avenue Edison, NJ, USA) using a fresh whole blood sample. The instrument is portable and intended for point-of-care use. HEMOCHRON® Jr. is a registered trademark of International Technidyne Corporation in the United States and other jurisdictions.[17] Peak anti-Xa activity levels correspond to peak ACT-LR. ACT-LR exceeding 150 s always corresponded to an anti-Xa level exceeding 0.5 U/mL.[17,22]

Anti-Xa activity in plasma was measured using chromogenic assays with enoxaparin standards (Instrumentation Laboratory Company, Lexington, MA, USA). Blood samples were placed into a Diatube (3.2% sodium citrate). The tubes were centrifuged at 3000 *g* for 15 min at 15°C within 30 min following venipuncture in order to obtain platelet-poor plasma, which was then immediately frozen at −80°C. The Heparin Kit

is an assay based on a synthetic chromogenic substrate and factor Xa inactivation. An automated chromogenic assay was performed for the quantitative determination of unfractionated heparin and LMWH activity in human citrated plasma. The conventional therapeutic range of anti-Xa levels was considered to be between 0.5 and 1.2 IU/mL.

Statistical Analyses

All continuous data were tabulated as mean ± SEM. Baseline ACT-LR data were analyzed using by the Kruskal–Wallis test. Continuous data were also analyzed using the Wilcoxon rank sum test, and a categorical data chi-square test, Fisher's exact test, or McNemar's test, wherever appropriate. The level of statistical significance was set at a p-value of less than 0.05. Data were analyzed using the SAS software for Windows (Statistical Analysis System, version 9.1, SAS Institute, Cary, NC, USA).

RESULTS

A total of 76 HD patients were recruited into the study; they were followed during a total of 11,856 consecutive dialyses. Sixty-two patients were randomly selected to receive nadroparin and 14 patients were randomly selected to receive enoxaparin. The baseline characteristics of the patients in the two treatment groups were similar and are shown in Table 1. All patients had previously been using unfractionated heparin. No association existed between the two groups and variables such as age, sex, body mass index, etiology of end-stage renal disease, HD duration, blood pressure, platelet count, hemoglobin, native arteriovenous fistula, and membrane materials of artificial kidney were not significantly different ($p > 0.05$).

Clinical Safety and Bleeding/Adverse Effect

Comparison of clinical safety between nadroparin and enoxaparin groups is shown in Table 2. We found no significant differences in optimum LMWH dosage between the two groups ($p = 0.500$). The incidence of bleeding and adverse events was 24.2% (15/62) in patients using nadroparin. The bleeding site included subcutaneous minor bleeding (11/15), subjunctive bleeding (2/15), vascular access bleeding (1/15), and hemorrhoid bleeding (1/15). The largest subcutaneous bleed occurred over the right inguinal area and was about 50 cm ×19 cm in size and did not require transfusion. The incidence of minor bleeding was 14.3% (2/14) in patients using enoxaparin. Only minor subcutaneous bleeding was observed. There were no significant differences in the occurrence of bleeding or adverse events between the two groups. Two patients switched from LMWH to unfractionated heparin due to general discomfort (one using nadroparin) and easy bleeding from the puncture site (one using enoxaparin). The incidence of excess usage of nadroparin dosage was 21.0% (13/62) and that of enoxaparin dosage was 7.1% (1/14) in HD patients. There were no significant differences with regard to the excess usage of LMWHs dosage between the two groups ($p = 0.445$). No major bleeding or mortality was found.

Table 1. Baseline patient characteristics of those using nadroparin and enoxaparin.

Patient characteristics	Nadroparin ($n = 62$)	Enoxaparin ($n = 14$)	p-Value
Age mean in years	58.4 ± 11.0	55.8 ± 13.2	0.578
Sex (male)	23 (37.1%)	8 (57.14%)	0.168
Mean body mass index	23.3 ± 3.7	23.2 ± 3.3	0.904
Body mass index >25	23 (37.1%)	3 (21.4%)	0.357
Etiology of end-stage renal disease			
Glomerulonephritis	38 (61.3%)	8 (57.1%)	0.586
Diabetic nephropathy	17 (27.4%)	3 (21.4%)	
Hypertension	5 (8.1%)	3 (21.4%)	
Lupus nephritis	1 (1.6%)	0	
Obstructive uropathy	1 (1.6%)	0	
Hemodialysis duration (months)	118.1 ± 58.2	95.1 ± 44.0	0.231
Systolic blood pressure (mmHg)	143.3 ± 32.0	134.3 ± 34.7	0.345
Diastolic blood pressure (mmHg)	77.1 ± 15.6	69.9 ± 14.8	0.086
Platelet count ($\times 10^4/\mu L$)	202.3 ± 63.2	212.0 ± 61.1	0.499
Hemoglobin (g/dL)	10.9 ± 1.4	11.5 ± 1.7	0.096
Native arteriovenous fistula	56 (90.3%)	13 (92.9%)	1.0
Membranes materials of artificial kidney			
Polysulfone	38 (61.3%)	7 (50%)	0.500
Cellulose triacetate	13 (21.0%)	5 (35.7%)	
Others	11 (17.7%)	2 (14.3%)	

Table 2. Comparison of safety and efficacy between nadroparin and enoxaparin groups.

	Nadroparin ($n = 62$)	Enoxaparin ($n = 14$)	p-Value
Mean LMWHs dose, anti-Xa IU/each HD	3937.9 ± 970.8	3714.3 ± 1204.4	0.500
Bleeding and adverse event	15 (24.2%)	2 (14.3%)	0.723
Subcutaneous bleed	11	2	
Subconjunctival bleeding	2	0	
Vascular access bleeding	1	0	
Hemorrhoid bleeding	1	0	
Extracorporeal circuit thrombosis	14 (22.6%)	2 (14.3%)	0.721
Artificial kidney clot (medium, pink)	13	2	
The lines and the bubble catcher (minimal clot)	1	1	
Excessive LMWH dosage patients	13	1	0.445

Note: LMWH, low-molecular-weight heparin; HD, hemodialysis.

Anticoagulation Efficacy

A comparison of the anticoagulation efficacy of nadroparin and enoxaparin groups is shown in Table 2. The incidence of extracorporeal circuit thrombosis was 22.6% (14/62) in patients using nadroparin. The extracorporeal circuit thrombosis included artificial kidney clot (medium, pink dialyzer) (13/14) and the lines/the bubble catcher minimal clot (1/14). The incidence of extracorporeal circuit thrombosis was 14.3% (2/14) in patients using enoxaparin. The extracorporeal circuit thrombosis included only artificial kidney clot (medium, pink dialyzer) (2/2). There were no significant differences in extracorporeal circuit thrombosis between the two groups ($p = 0.721$).

Pharmacokinetic and ACT-LR/Anti-Xa Activity

A comparison between ACT-LR and anti-Xa levels of nadroparin and enoxaparin groups is shown in Table 3. There was no significant difference in ACT-LR and anti-Xa levels at baseline (before HD), after 1, 2, and 3 h, and at the end of HD in both groups ($p > 0.05$). Baseline ACT-LR for those in the control group ($n = 24$) were 64.7 ± 4.7 s, in nadroparin group ($n = 62$) 69.3 ± 10.0 s, and in enoxaparin group ($n = 14$) 67.1 ± 8.2 s. There was no significant difference observed between the three groups ($p = 0.169$).

ACT-LR correlated significantly with anti-Xa levels ($r = 0.790$, $p < 0.0001$) after 2 h of HD for patients in the group that received nadroparin. ACT-LR also correlated significantly with anti-Xa levels ($r = 0.568$, $p = 0.034$) after 2 h of HD for patients in the group that received enoxaparin. Figure 1 shows ACT-LR during HD in patients receiving nadroparin or enoxaparin. ACT-LR was determined before HD, after 1, 2, and 3 h, and at the end of HD. Figure 2 shows anti-Xa

Table 3. Comparison of ACT-LR values and anti-Xa activity between nadroparin and enoxaparin groups.

	Nadroparin ($n = 62$)	Enoxaparin ($n = 14$)	p-Value
ACT-LR (s)			
ACT-LR (before HD)	69.3 ± 10.0	67.1 ± 8.2	0.555
ACT-LR (after 1 h HD)	145.0 ± 98.7	114.1 ± 32.2	0.555
ACT-LR (after 2 h HD)	102.0 ± 64.2	94.5 ± 21.6	0.649
ACT-LR (after 3 h HD)	83.6 ± 22.4	80.4 ± 14.0	0.941
ACT-LR (at the end of HD)	72.4 ± 13.5	72.2 ± 8.9	0.653
Anti-Xa levels (IU/mL)			
Anti-Xa (before HD)	0.02 ± 0.03	0.01 ± 0.00	0.527
Anti-Xa (after 1 h HD)	0.63 ± 0.27	0.61 ± 0.31	0.678
Anti-Xa (after 2 h HD)	0.49 ± 0.24	0.50 ± 0.24	0.947
Anti-Xa (after 3 h HD)	0.37 ± 0.20	0.36 ± 0.20	0.936
Anti-Xa (at the end of HD)	0.26 ± 0.17	0.26 ± 0.19	0.963

Note: ACT-LR, low-range activated clotting time; HD, hemodialysis.

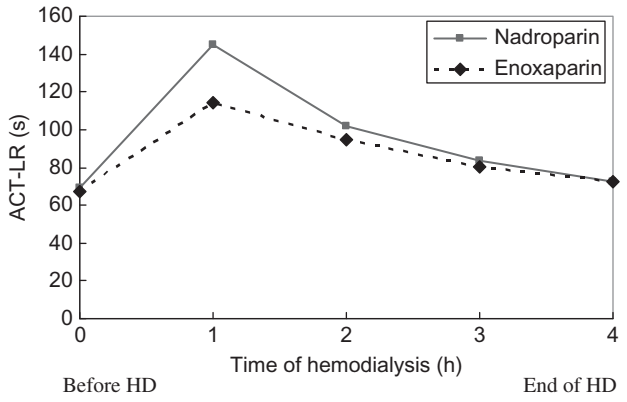

Figure 1. ACT-LR during HD in patients receiving nadroparin or enoxaparin. ACT-LR (s) was determined before HD, after 1, 2, and 3 h, and at the end of HD.

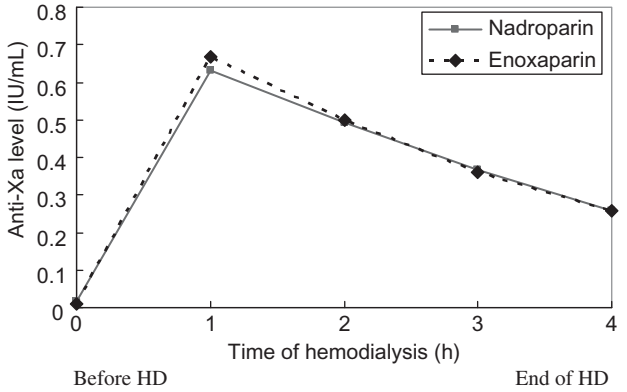

Figure 2. Anti-Xa levels during HD in patients receiving nadroparin or enoxaparin. Anti-Xa levels were determined before HD, after 1, 2, and 3 h, and at the end of HD.

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Excessive Dosage of Nadroparin and Enoxaparin

The excessive LMWHs dosage had 14 patients including 13 using nadroparin and 1 using enoxaparin. Only one excessive-dosage patient used enoxaparin 4000 anti-Xa IU/HD (80 IU/kg) and checked ACT-LR of 121 s but subcutaneous bleed occurred. The bleed improved after enoxaparin dosage reduced to 3000 anti-Xa IU (60 IU/kg). A comparison of safety, efficacy, ACT-LR, and anti-Xa levels between excessive and reduced dosage groups in the same patient using nadroparin is shown in Table 4. We found significant differences in mean dosage, cost, bleeding/adverse effect, and extracorporeal circuit thrombosis between excessive and reduced nadroparin dosage groups ($p < 0.05$). There was significant difference in ACT-LR and anti-Xa levels after 1, 2, and 3 h HD between excessive and reduced nadroparin dosage groups ($p < 0.05$).

DISCUSSION

We know that LMWHs are increasingly used for chronic HD and have advantages over fractionated heparins.[8–11] LMWHs are routinely used in HD in European clinical settings.[23] Bernieh et al.[24] reported that enoxaparin had been routinely used for 7 years. Lim et al.[7] reported about the safety and efficacy of LMWHs for use in HD in patients with end-stage renal failure. A previous report revealed few details about the direct comparison of two different LMWHs for use in HD patients.[14–16] However, no study compared the safety and efficacy of nadroparin and enoxaparin for HD patients except for one animal study.[25] Unfractionated heparin is still routinely used in Taiwan as well as North America.[19] We do not routinely prescribe LMWH in regular HD procedures because of its higher cost. Indications for the necessity of usage of LMWH are in the patients who need large dosage of heparin or have an allergy or general discomfort to conventional heparin.

The main advantage of LMWH over unfractionated heparin in HD is that one predialysis intravenous bolus injection is sufficient to perform the procedure.[3,26] Previous reports indicate that a single bolus dose of enoxaparin (typically 0.8 mg/kg) was adequate for >98% patients dialyzing for up to 6 h. However, some patients required a second bolus dose; these patients were treated by giving a lower initial bolus (typically 0.4 mg/kg) followed by a second bolus injection after 3 h.[24] In our study, a single bolus dose of enoxaparin (average 0.60 mg/kg or 62.5 IU/kg) was adequate (13/14) for >92% of patients during HD. Only one patient needed the second bolus dose. The patient was treated by giving an initial bolus injection of enoxaparin (0.5 cc or 50 mg) followed by a second bolus injection (0.1 cc or 10 mg) after 3 h for a total of 60 mg (about 0.88 mg/kg) due to easy artificial kidney clot. A single bolus dose of nadroparin (average 67 IU/kg) was adequate for 100% (62/62) of patients during HD. So, nadroparin provides adequate anticoagulation for HD using single bolus injections at relatively low doses.

Unlike unfractionated heparin, there is currently no readily available bedside test of LMWH anticoagulant activity. However, in routine clinical practice of outpatient HD, most centers do not regularly monitor ACT-LR or anti-Xa activity.[27] We simply increased the bolus dose if a clot was observed in the dialyzer or venous air detector chamber. We reduced dosages if the times for needle puncture sites to stop bleeding exceeded 15 min. ACT-LR exceeding 150 s always corresponded to

Table 4. Comparison of safety, efficacy, ACT-LR values, and anti-Xa activity between excessive and reduced dosage groups in same patients using nadroparin.

Patient characteristics/nadroparin	Excessive dosage ($n = 13$)	Reduced dosage ($n = 13$)	p-Value
Mean nadroparin dose (IU/HD)	4896.2 ± 1014.8	3946.2 ± 1014.8	<0.001
Mean nadroparin dose (IU/kg/HD)	80.3 ± 13.6	64.3 ± 13.3	<0.001
Mean nadroparin cost/HD (dollars) (NT)	165.9 ± 39.9	132.5 ± 39.2	<0.001
Bleeding and adverse effect	5 (38.5%)	0 (0%)	0.025
Extracorporeal circuit thrombosis	6 (46.2%)	0 (0%)	0.014
ACT-LR (s)			
ACT-LR (before HD)	75.5 ± 12.6	71.3 ± 9.98	0.086
ACT-LR (after 1 h HD)	275.8 ± 146.1	165.7 ± 54.4	0.001
ACT-LR (after 2 h HD)	160.8 ± 122.2	112.4 ± 34.1	0.001
ACT-LR (after 3 h HD)	111.4 ± 34.1	92.8 ± 21.6	<0.001
ACT-LR (at the end of HD)	86.9 ± 19.5	80.6 ± 17.9	0.060
Anti-Xa levels (IU/mL)			
Anti-Xa (before HD)	0.04 ± 0.06	0.01 ± 0.01	0.244
Anti-Xa (after 1 h HD)	0.99 ± 0.26	0.74 ± 0.20	<0.001
Anti-Xa (after 2 h HD)	0.75 ± 0.27	0.63 ± 0.21	0.023
Anti-Xa (after 3 h HD)	0.59 ± 0.24	0.48 ± 0.18	0.034
Anti-Xa (at the end of HD)	0.45 ± 0.21	0.35 ± 0.18	0.052

Note: ACT-LR, low-range activated clotting time; HD, hemodialysis; NT, new Taiwan.

an anti-Xa level exceeding 0.5 U/mL.[17,22] Peak anti-Xa activity levels correspond to peak ACT-LR. So in our study, if ACT-LR exceeds 150 s or a baseline 2.5-fold after 1 or 2 h of HD initially at bedside, we suggest the evaluation and optimization of LMWH dosage depending on the desirable effect of anticoagulation by titrating the dosage of enoxaparin or nadroparin to 0.1 cc per session if prolonged ACT-LR was checked or any observable adverse events occur.

It may be necessary to reduce the LMWH dosage in next HD. Previous reports revealed that the optimum nadroparin dosage was between 64 and 70 IU/kg or 4100 IU/session in HD patients.[12,28,29] The previous reports also revealed that the optimum enoxaparin dosage was between 0.36 and 0.7 mg/kg in HD patients.[24,30] In our study, LMWH (0.4 cc) was given if body weight was <60 kg, or 0.6 cc if body weight was >60 kg. The dosage of nadroparin necessary to prevent clotting of the extracorporeal circuit was an average of 67.5 ± 19.3 IU/kg or 3937.9 ± 970.8I U/session. These figures are consistent with previous reports.[12,28,29] The dosage of enoxaparin was an average of 0.6 mg/kg/session or 3714.3 ± 1204.4 IU/session in our study. The results were similar to previous reports.[24,30] In excessive LMWHs dosage portion, 85.7% (12/14) patients had ACT-LR exceeding baseline 2.5-fold and anti-Xa level exceeding 0.5 U/mL after 1 or 2 h of HD. It is of interest that two patients (one using nadroparin, one using enoxaparin) had clinical bleed but ACT-LR less than 150 s and anti-Xa level not over 0.5 U/mL after 1 or 2 h of HD. We did not use protamine for excessive LMWH dosage due to encountering only minor bleeding over the course of our study. We propose that the safe therapeutic range of ACT-LR is less than 150 s or baseline 2.5-fold and that the safe therapeutic range for anti-Xa level is not over 0.5 U/mL after 1 or 2 h of HD.

Stefoni et al.[12] reported that no bleeding episode was observed in patients using nadroparin. Nurmohamed et al.[6] reported that 8.6% (3/35) of minor bleeding episodes were observed in patients who were subjected to procedures that involved nadroparin. Vavenport[23] reported that chronic HD patients routinely use enoxaparin and experienced only one bleeding episode in 2 years. Bernieh et al.[24] reported that 0.4% bleeding episodes were observed in patients that were given enoxaparin. Saltissi et al.[3] also reported that 33.3% (12/36) of bleeding episodes including 1 severe and 11 moderate were observed in patients with an initial dose of 1 mg/kg enoxaparin that was then titrated to 0.69 mg/kg. Previous reports revealed that most bleeding events were minor and tended to occur at vascular access sites.[3,6,12] In our study, the incidence of bleeding and adverse events was 24.2% (15/62) in patients using nadroparin. These findings are higher than those of previous reports.[6,12] The incidence of minor bleeding was 14.3% (2/14) in patients using enoxaparin. This value is between two previously reported values ranging from 0.4% to 33%.[3,23,24] Only one patient suffered minor bleeding at the vascular access site. The majority of minor bleeding occurred in the subcutaneous area. This is different from previous reports.[3,6,12] There were no significant differences in bleeding and adverse events between the two groups. Usage of a LMWH-induced whole-general disorder or allergy is rare.[15] Two patients changed LMWH to unfractionated heparin due to general discomfort (one using nadroparin) and easy bleeding from the puncture site (one using enoxaparin). It is possible that some HD patients do not know when intermittent subcutaneous bleeding occurs due to excessive LMWH dosages. In general, patients that experience bleeding disorders improve after their LMWH dosages are reduced. We suggest that clinical evaluation is necessary after usage of LMWH.

Stefoni et al.[12] reported no extracorporeal circuit thrombosis in patients using nadroparin. Nurmohamed et al.[6] reported a rate of occurrence between 0% and 7% of extracorporeal circuit thrombosis in patients using nadroparin. Bernieh et al.[24] reported a 0.8% rate of occurrence of extracorporeal circuit thrombosis in patients using enoxaparin. Saltissi et al.[3] reported a rate of occurrence of 1.53% (17/1111) in regards to extracorporeal circuit thrombosis in patients using enoxaparin. Finally, in our study, the incidence rate of extracorporeal circuit thrombosis was 22.6% (14/62) in patients using nadroparin. Obviously, these rates are much higher than those observed in previous reports.[6,12] The incidence rate of extracorporeal circuit thrombosis was 14.3% (2/14) in patients using enoxaparin. This rate is also higher than that of previous reports.[3,24] There were no significant differences in extracorporeal circuit thrombosis between the two groups included in our study. The majority of extracorporeal circuit thrombosis belonged to medium, pink artificial kidney clot after the careful evaluation and observation by nursing staff. The patients with extracorporeal circuit thrombosis had an increased LMWH dosage or an initial LMWH dosage including heparin in the amount of 3000 or 5000 U in the form of a rinse. The possible reasons of high rate of bleeding and thrombosis were initial usage of LMWH with excessive dosage, high dosage LMWH over 0.5 cc in each session, high-risk-group patients, and detailed close evaluation with observation. We suggest that if extracorporeal circuit thrombosis is found, the patient's LMWH dosage can be increased or the patient can be given the initial LMWH dosage with a heparin dosage of 3000 or 5000 U rise.

Different LMWHs had different pharmacokinetic and biological properties.[19–21] As a result, it is possible that the pharmacokinetic and structural profiles of different LMWHs could result in different efficacy and safety profiles for HD patients. However, it is clinically important to recognize that each LMWH is

a distinct therapeutic entity. Moreover, different hospitals or countries have different clinical experience with LMWHs and as a result different dosage adjustments may be recommended or adverse effects may be noted. Every HD patient was given a different dosage of LMWH that was determined according to the previously measured ACT-LR or anti-Xa activity. Both LMWHs, nadroparin and enoxaparin, have similar pharmacokinetic profiles. In our study, the comparison of clinical safety between nadroparin and enoxaparin groups showed no significant differences. In addition, the comparison of ACT-LR and anti-Xa levels between nadroparin and enoxaparin groups showed no significant differences. This study not only showed equivalence between nadroparin and enoxaparin in terms of efficacy but both LMWHs were also found as to be equivalently safe. However, clinical observation is important in high-risk-group patients. In the group of excessive dosage of LMWHs, it could reduce average 19.4% LMWHs dosage in each HD session to promote patient's safety and decrease HD cost relatively.

A limitation of our study is that our chronic HD patients were about 800 and only around 20% of those patients used LMWH. Second, our study group included around 47.5% of total HD patients using LMWHs. As a result, our study group may be considered to be quite small and was limited by the overall financial impact.

In conclusion, LMWH is not still routinely used due to its high cost in Taiwan. As previously noted, our study showed that both LMWHs, nadroparin and enoxaparin, are safe and effective for chronic HD patients. LMWHs could be adjusted to achieve minimal but effective dosage to promote patient's safety and decrease HD cost in HD patients with excessive dosage.

ACKNOWLEDGMENTS

We thank our patients for contributing samples for this study. The technical assistance from Miss Po-Shan Chiang is deeply appreciated. This study was supported by Chang Gung Memorial Hospital CMRP, grant number CMRPG880901.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible the content and writing this paper.

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