Efficacy and Safety of Enoxaparin during Hemodialysis: Results from the HENOX Study

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Background: *Low molecular weight heparins (LMWHs) have been suggested as an anticoagulant in hemodialysis (HD) since they provide convenient usage, safety and effective outcomes.*
Objective: *Determine clinical efficacy and safety of enoxaparin sodium for the anticoagulation effect during HD in 99 clinically stable end-stage renal disease (ESRD) patients.*
Material and Method: *This prospective open-label study was conducted in seven hemodialysis centers in Thailand. HD prescription during the present study was similar to the previous prescriptions including the type of dialyzer. Enoxaparin sodium 0.7 mg/kg was administered into a pre-dialyzer arterial line at the beginning of the HD session. The anticoagulation effect was monitored by visual inspection of the HD line hourly and inspection of the dialyzer at the end of HD session. Vascular access compression time was monitored at both arterial and venous sites separately at the end of the HD.*
Results: *HD with enoxaparin sodium resulted in no fibrin/clot formation in a hemodialysis line in 97 cases (98%), and no significant clot formation in a dialyzer in 96 cases (97%). The mean vascular compression time was 5.63 $\pm$ 1.90 minutes at the arterial site and 5.72 $\pm$ 2.61 minutes at the venous site. Neither major adverse events nor major hemorrhages were reported. Prolonged activated partial thromboplastin times (aPTT) at 30 minutes after hemodialysis were reported in two cases. These abnormal aPTT cases returned to normal levels within 24 hours and 72 hours, respectively.*
Conclusion: *The present study suggests that a single-dose regimen of enoxaparin sodium 0.7 mg/kg is an effective, well-tolerated, and convenient alternative to sodium heparin.*

Keywords: *Enoxaparin sodium, Hemodialysis, ESRD, Anticoagulant*

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The formation of a fibrin clot in a dialyzer and/or a blood line during a hemodialysis (HD) session is a frequent and undesired occurrence. Unfractionated heparin has widely been used as an anticoagulant in HD. Although standard systemic heparinization in HD is relatively safe and effective, long term heparin use is still associated with several complications, including thrombocytopenia[1], platelet dysfunction[2], lipid abnormalities[3], allergic reactions, osteoporosis[4], and an increased risk of hemorrhage[5]. Low molecular weight heparins (LMWHs) have been introduced in clinical practice with evidence of potential therapeutic advantages over unfractionated heparin[6,7]. Differences in the binding properties convey pharmacokinetic advantages[8,9], simple dosing, more predictable anticoagulant activity[10], and an improved safety profile for LMWH over unfractionated heparin. Compared with unfractionated heparin, LMWHs

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bind less to endothelial cells and plasma proteins, resulting in improved bioavailability. The renal clearance of LMWHs is slower than the hepatic uptake. Consequently, the elimination half-life of LMWHs is much longer than that of unfractionated heparin, which is one of the factors that allows LMWHs to be dosed at longer intervals[9].

Regarding the efficiency of anticoagulation, there are several studies comparing a variety of LMWHs with unfractionated heparin in hemodialysis patients, but the experience with enoxaparin sodium in this indication is limited. Therefore, the authors conducted the present prospective, an open-label study that aimed to determine the clinical efficacy and safety of enoxaparin sodium for anticoagulation during HD sessions in hemodialysis patients.

Material and Method

Patients and Study design

Ninety-nine adult patients (54 male, 45 female) who suffered from end-stage renal disease (ESRD) requiring maintenance hemodialysis were recruited into the present study (Table 1). All subjects had a stable hemodialysis setting prescription using unfractionated heparin at least 1 month before entering into the present study. Written informed consent was obtained from all participants. Patients received hemodialysis 2-3 sessions weekly for 4-5 hours per session with a dialysis blood flow of 250-350 ml/min. The vascular access of ESRD patients was either a native arterio-venous fistula (AVF) or an arterio-venous graft (AVG). Patients with known bleeding disorders or who had contraindications for anticoagulants were excluded from the present study. Subjects receiving any other forms of anticoagulant therapy were also excluded. All patients were asked to continue their regular medications (including lipid-lowering and anti-hypertensive therapy) and were regularly treated during the study period. Eligible subjects were assigned to receive a single intravenous bolus dose of 0.7 mg/kg of enoxaparin sodium into the pre-dialyzer arterial line of the extracorporeal circuit at the beginning of the dialysis session. Anticoagulation was monitored by visual inspection of blood clots in the arterial blood line hourly and in the hemodialyser at the end of the hemodialysis session.

Clinical monitoring

To assess the efficacy of anticoagulation, the degree of fibrin and clot formation in the blood line was graded on a 4-point scale: grade 1 showed no clot, grade 2 showed a fibrin formation, grade 3 showed partial clot formation, and grade 4 showed definite clot formation. Coagulation in the blood line was evaluated every hour after flushing 100 ml of normal saline solution into the blood line. The degree of clot formation in the dialyzer was graded into a 4-point scale: grade 1 indicating clean filter, grade 2 with blood stripes less than 5% of the fibers seen at the cut surface of the dialyzer, grade 3 with blood stripes more than 5% of the fibers seen at the cut surface of the dialyzer, and grade 4 with a coagulated filter. Coagulation assessment in the dialyzer was carried out after manual irrigation with 1000 ml of normal

Table 1. Patients' characteristics in 99 cases

Characteristics	Mean ± SD or percent
General characteristics	
Gender	
Male	54.5%
Female	45.5%
Age (years)	49.46 ± 12.30
BMI (kg/m^2)	21.73 ± 3.61
Hct (%)	32.03 ± 5.09
Hb (g/dl)	10.62 ± 1.74
Mean arterial BP (mmHg)	99.70 ± 15.58
Cause of ESRD	
DM	22.2%
Non-DM	77.8%
Type of vascular access	
AVF	87.9%
AVG	12.1%
Site of vascular access	
Forearm	65.3%
Upper arm	34.7%
Frequency of hemodialysis	
2 times/week	67.7%
3 times/week	32.3%
Hemodialysis prescription	
Types of dialyzer	
Cellulose triacetate	78.8%
Polysulfone	21.2%
Flux	
High flux	89.9%
Low flux	10.1%
Weight before HD (Kg)	55.48 ± 10.18
Mean flow rate (ml/min)	354.93 ± 81.12

SD = standard deviation; ESRD = end stage renal disease; DM = diabetes mellitus; BP = blood pressure; AVF = arterio-venous fistula; AVG = arterio-venous graft; HD = hemodialysis

saline solution after finishing the HD session. Blood pressure, pulse rate, and abnormal symptoms such as cramps or abnormal bleeding were recorded hourly during HD. Post HD hemostasis was assessed by recording compression time at the arterial and venous side with a stopwatch, and observing the time from needle removal to spontaneous bleeding cessation from puncture sites.

Laboratory estimations

Laboratory assessment of liver function, platelet count and coagulation time were performed twice at two weeks before entry into the present study and in the morning of the present study day, to exclude patients with any bleeding disorders. The aPTT tests were done before starting hemodialysis session and repeated at 30 minutes after the hemodialysis session.

Statistical methods

The significance of differences between groups was determined using analysis of variance (ANOVA) for parametric data or Kruskal-Wallis ANOVA on ranks for non-parametric data, as appropriate. Paired data was compared by using the paired-t-test. Unpaired t-test was used to compare between two groups or non-parametric data was compared using the Mann-Whitney U-test as appropriate. The significance of proportions was assessed by the z-test. A p-value < 0.05 was considered significant. Data are expressed as mean $\pm$ standard deviation (SD) except where otherwise indicated.

Results

The present study was designed as a prospective one arm, open-label study, with patients assigned to receive enoxaparin sodium (Clexane®, sanofi-aventis, Paris, France) as an anticoagulant. Ninety-nine patients (male 54 and female 45) enrolled in the present study. The mean age of the patients was 49.46 $\pm$ 12.30 years. There were 22 ESRD patients with diabetic nephropathy. Eighty-seven ESRD patients (87.9%) had AVF as a vascular access for hemodialysis (Table 1).

Concomitant diseases included hypertension (80.8%), dyslipidemia (23.2%), diabetes mellitus (DM) (22.2%), gouty arthritis (10.1%), chronic glomerulonephritis (8.1%), systemic lupus erythematosus (SLE) (3%), and polycystic kidney, hydronephrosis or IgA nephropathy (1%). Eighty-eight percent of the patients received folic acid and erythropoietin, 83.8% received calcium carbonate, 76.8% received sodium bicarbonate, and 65.7% received ferrous supplement.

Overall, 95% of dialysis sessions were performed without the appearance of only a non-significant clot in dialyzers or blood lines. Two cases with grade 3 clot formation in a blood line were found with one case in the fourth hour and another one in the fifth hour respectively (Fig. 1). Three cases of grade 3 clot formation in a dialyzer (blood stripes more than 5% of fibers seen at the surface area of dialyzer) were found (Table 2, Fig. 2).

Patients with clot formation in a blood line and a dialyzer had some characteristics that differed from patients without clot formation. The mean arterial blood pressure before HD of patients without clot formation was 100.63 $\pm$ 3.5 mmHg. The mean arterial blood pressure after HD of patients without clot formation was 100.69 $\pm$ 3.1 mmHg compared with 74.20 $\pm$ 3.2 mmHg in patients with clot formation ($p < 0.001$). The mean duration of HD was 4.29 $\pm$ 0.44 hours in patients without clot formation while the mean duration in patients with clot formation was 4.61 $\pm$ 0.55 hours

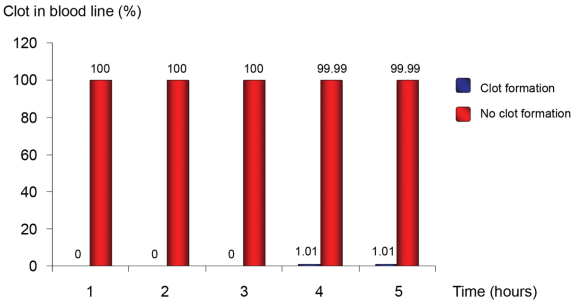

Fig. 1 Clot in blood line in different points of time

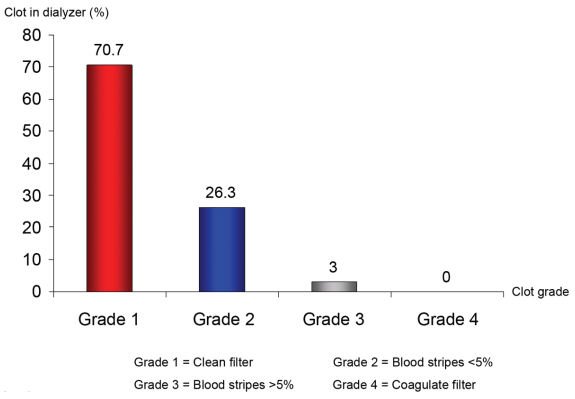

Fig. 2 Clot in dialyzer

($p < 0.001$). The activated partial thromboplastin time (aPTT) ratio (aPTT before HD/aPTT after HD) in patients without clot formation was 1.13 ± 0.76 compared with 0.99 ± 0.14 in patients with clot formation ($p = 0.074$) (Table 3).

The measure of hemostasis at the vascular access was obtained by recording vascular access compression time at the end of the HD session with a stop-watch. Vascular access compression time at arterial site was 5.63 ± 1.90 minutes compare with 5.72 ± 2.61 minutes at venous site.

There was no report of any hemorrhage during any HD session. Prolonged aPTTs at 30 minutes after HD were reported in two cases with no clinical bleeding. The abnormal aPTT returned to a normal range within 24 and 72 hours, respectively. Neither serious adverse event nor any hemorrhage was reported.

Table 2. Clot formation

Clot formation	n (%)
Clot in blood line	
Clot	2 (2)
No-clot	97 (98)
Clot in dialyser	
Grade 1: clean filter	70 (70.70)
Grade 2: blood stripes < 5% of surface area of dialyser	26 (26.30)
Grade 3: blood stripes ≥ 5% of surface area of dialyser	3 (3)
Grade 4: coagulated filter	0

Table 3. Blood clot formation in blood line and dialyzer

	Without clot formation (n = 97)	With clot formation (n = 99)	p-value
Arterial blood pressure (mmHg)			
before HD	100.63 ± 3.5	-	-
after HD	100.69 ± 3.1	74.20 ± 3.2	<0.001
Duration of HD	4.29 ± 0.44	4.61 ± 0.55	<0.001
aPTT ratio	1.13 ± 0.76	0.99 ± 0.14	0.074

HD = hemodialysis; aPTT = the activated partial thromboplastin time

Discussion

The ease of administration (single bolus pre-dialyzer) and lack of need for laboratory monitoring seems to be the advantages of LMWHs over standard unfractionated heparin in prophylaxis extracorporeal circuit coagulation during hemodialysis. The dosage of enoxaparin used in the present study was similar to that used in the study by Saltissi et al, which was a lower dosage of enoxaparin than the manufacturer's recommendation[11]. That particular study used an initiating dose of enoxaparin at 1 mg/kg and reduced it when there was any hemorrhagic complication. It has been previously reported that there were 94% clot free cases in all HD sessions with 4.5% of hemorrhagic complication and 0.1% of thrombosis during HD with a titrated dose of enoxaparin. Our current study reported two cases with a significant clot formation in a blood line with one case in the fourth hour and another one in the fifth hour respectively (Fig. 1) and three cases with a grade 3 clot formation in the dialyzer at the end of the HD session. No significant clot formation in either a blood line or the dialyzer was observed in 95% of cases. All subjects had normal vascular access compression times and no abnormal bleeding was reported during HD. The high efficacy of a single bolus dose of enoxaparin at 0.7 mg/kg given at the beginning of HD from the present study is consistent with the previous study while causing less adverse events[11].

Enoxaparin sodium is a LMWH that acts as anti-IIa and anti-Xa coagulation factors, which are in the common pathway of coagulation cascades. Prolonged aPTT reflects the impairment of the intrinsic pathway, which cannot be explained by the action of LMWH. Previous studies demonstrated an increased risk of minor bleeding, *i.e.* from vascular access sites in a HD session with LMWHs more than UFH, but did not report abnormal aPTT[12]. There were a numbers of patient characteristics that differed between patients with and without any significant clot formation. The number of patients with a clot formation is too small to compare with those particular characteristics of the patients without significant clot because the present study was not designed to determine the differences between them. These data demonstrate possible associations that need further evaluation in well-designed studies for these particular objectives.

Future trials should be designed to compare LMWH with UFH as an anticoagulant for HD in ESRD patients. Thus, more direct comparisons of differences are also needed. For addressing the issue of bias, a randomized control trial should be considered. The anti-Xa level should be measured to document the level of anticoagulation.

Overall, the present study demonstrated the efficacy and safety of a single intravenous bolus dose of enoxaparin 0.7 mg/kg given at the beginning of HD. There is a limitation of the present study regarding the study design, which is a non-controlled study. However, recommendations on the choice of anticoagulant for ESRD patients who undergo HD will continue to need larger and more rigorous randomized controlled trials.

Potential conflict of interest

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References

1. Kelton JG. Heparin-induced thrombocytopenia. Haemostasis 1986; 16: 173-86.
2. Salzman EW, Rosenberg RD, Smith MH, Lindon JN, Favreau L. Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 1980; 65: 64-73.
3. Teraoka J, Matsui N, Nakagawa S, Takeuchi J. The role of heparin in the changes of lipid patterns during a single hemodialysis. Clin Nephrol 1982; 17: 96-9.
4. Griffith GC, Nichols G Jr, Asher JD, Flanagan B. Heparin osteoporosis. JAMA 1965; 193: 91-4.
5. Gotti E, Remuzzi G. Uremic bleeding: Clinical presentation and management. In: Remuzzi G, Rossi EC, editors. Hemostasis and the kidney. London: Butterworth; 1989: 131-41.
6. Holmer E. Anticoagulant properties of heparin and heparin fractions. Scand J Haematol Suppl 1980; 36: 25-39.
7. Nurmohamed MT, ten Cate H, ten Cate JW. Low molecular weight heparin(oid)s. Clinical investigations and practical recommendations. Drugs 1997; 53: 736-51.
8. Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119: 64S-94S.
9. Weitz JI. Low-molecular-weight heparins. N Engl J Med 1997; 337: 688-98.
10. Handeland GF, Abildgaard U, Holm HA, Arnesen KE. Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. Eur J Clin Pharmacol 1990; 39: 107-12.
11. Saltissi D, Morgan C, Westhuyzen J, Healy H. Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. Nephrol Dial Transplant 1999; 14: 2698-703.
12. 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: 3192-206.

ประสิทธิภาพและความปลอดภัยของยา Enoxaparin ในระหว่างการฟอกเลือดล้างไต: ผลการศึกษา HENOX

เกรียงศักดิ์ วารีแสงทิพย์, ศุภชัย ฐิติอาชากุล, อินทรีย์ กาญจนกุล, วสันต์ สุเมธกุล, อุดม ไกรฤทธิชัย, อนุตตร จิตตินันทน์, ดิเรก บรรณจักร

ภูมิหลัง: *Heparin โมเลกุลต่ำ ใช้ในการฟอกเลือดล้างไตในผู้ป่วยไตวายเรื้อรังระยะท้ายอย่างมีประสิทธิภาพ และมีความปลอดภัยในการใช้เป็น anticoagulant แต่ยังขาดข้อมูลของ heparin โมเลกุลต่ำในผู้ป่วยไตวายเรื้อรังไทยที่ได้รับการรักษาด้วยการฟอกเลือดล้างไต*

วัตถุประสงค์: *การศึกษานี้เป็น multicenter ศึกษาในผู้ป่วยไทย 99 ราย ที่ได้รับการรักษาด้วยการฟอกเลือดล้างไต*

วัสดุและวิธีการ: *ในการศึกษานี้ใช้ enoxaparin sodium 0.7 mg/kg ติดตามผลของ enoxaparin sodium โดยการดู blood clot ใน dialyzer และ blood line และจับเวลาที่ใช้ในการกดเพื่อให้เลือดหยุด หลังการฟอกเลือดล้างไต (vascular compression time)*

ผลการศึกษา: *ผู้ป่วย 97 ราย (ร้อยละ 98) ไม่พบการเกิด blood clot ใน dialyzer, vascular compression time ได้ 5.63 $\pm$ 1.9 นาที ทางด้าน artery และ 5.72 $\pm$ 2.61 นาที ทางด้าน vein ไม่มีผู้ป่วยรายใดมีปัญหาเลือดออก มีผู้ป่วย 2 ราย มีภาวะการแข็งตัวของเลือดผิดปกติ และภาวะการแข็งตัวของเลือดในผู้ป่วย 2 รายนี้กลับสู่ภาวะปกติในเวลา 24 และ 72 ชั่วโมงตามลำดับ*

สรุป: *การศึกษานี้ได้แสดงให้เห็นว่า enoxaparin sodium 0.7 mg/kg สามารถให้เป็น anticoagulant ในการฟอกเลือดล้างไตในผู้ป่วยไตวายเรื้อรังอย่างมีประสิทธิภาพ และปลอดภัย*