Effect of Low-dose Heparin Anticoagulation on Number of Dialyzer Reuse in Maintenance Hemodialysis: A Randomized Crossover Study

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Abstract

Background: Heparin is commonly used to prevent clotting of dialyzer in maintenance hemodialysis. Higher dose of unfractionated heparin may increase the risk of bleeding, whereas lower dose may increase the risk of clotting and limit the number of dialyzer reuse. The present randomized crossover study compared the efficacy and safety of low-dose heparin anticoagulation with standard-dose heparin anticoagulation in maintenance hemodialysis.

Method: Seventy five stable maintenance hemodialysis patients underwent 1:1 randomization to receive low-dose heparin anticoagulation protocol (LDP) (loading 15 units/kg and maintenance 500 units/hour) or standard-dose heparin anticoagulation protocol (SDP) (loading 50 units/kg and maintenance dose 1,000 units/hour). Primary outcome was the difference in the number of dialyzer reuse. Secondary outcomes were differences in activated partial thromboplastin time (aPTT), Kt/V, erythropoietin and iron requirements, iron parameters and adverse events.

Results: The number of dialyzer reuse was significantly lower in the LDP group compared with the SDP group (17±4 vs. 13±5 treatments, $p<0.001$). LDP group had lower aPTT values at 2 hours (36±13 vs. 70±36 seconds, $p<0.001$) and 4 hours (31±10 vs. 55±30 seconds, $p<0.001$) after dialysis initiation and Kt/V (1.7±0.4 vs. 1.9±0.4, $p=0.001$) compared with SDP group. Hemoglobin was higher in the LDP group. There were no differences in erythropoietin and iron requirements and iron parameters. Two minor bleeding at the vascular access site occurred in the SDP group. Other minor adverse events were not different between the two groups.

Conclusion: Using low-dose heparin anticoagulation resulted in a lower number of dialyzer reuse compared with standard-dose heparin. The negative impact on dialysis adequacy was also evident. Thus, low-dose heparin anticoagulation should not be recommended in the prevention of dialyzer clotting in maintenance hemodialysis patients with low risk of bleeding.

Keywords: anticoagulation; heparin; dialysis; dialyzer; kidney failure; TCV; ESRD; ESKD

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ผลของการใช้ยาต้านการแข็งตัวของเลือดเฮพารินขนาดต่ำต่อจำนวนการใช้ตัวกรองซ้ำในการฟอกเลือดด้วยเครื่องไตเทียม: การศึกษาแบบสุ่มและข้ามกลุ่ม

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บทคัดย่อ

บทนำ: การใช้เฮพารินเพื่อป้องกันการแข็งตัวของเลือดภายในตัวกรอง เป็นมาตรฐานในการฟอกเลือดด้วยเครื่องไตเทียม การใช้เฮพารินในขนาดสูงอาจส่งผลให้เกิดเลือดออกเพิ่มขึ้น ในขณะที่ถ้าใช้เฮพารินในขนาดต่ำ อาจเพิ่มการแข็งตัวของเลือดภายในตัวกรอง ทำให้สามารถใช้ตัวกรองซ้ำ (dialyzer reuse) ได้ในจำนวนครั้งที่ลดลง การศึกษานี้เป็นการศึกษาแบบสุ่มและข้ามกลุ่ม (randomized crossover) เพื่อเปรียบเทียบประสิทธิภาพและความปลอดภัยของการใช้เฮพารินขนาดต่ำกับขนาดมาตรฐาน ในการป้องกันการแข็งตัวของเลือดในตัวกรองในการฟอกเลือดด้วยเครื่องไตเทียม

ระเบียบวิธีวิจัย: ผู้ป่วยฟอกเลือดด้วยเครื่องไตเทียมจำนวน 75 คน ได้รับการสุ่มเพื่อรับเฮพารินขนาดต่ำ (loading 15 ยูนิต/กิโลกรัม และ maintenance 500 ยูนิต/ชั่วโมง) หรือ ขนาดมาตรฐาน (50 ยูนิต/กิโลกรัม และ maintenance 1,000 ยูนิต/ชั่วโมง) โดยมีวัตถุประสงค์หลัก คือ ความแตกต่างของจำนวนครั้งของการใช้ตัวกรองซ้ำ และวัตถุประสงค์รอง คือ ความแตกต่างของ activated partial thromboplastin time (aPTT), Kt/V, ขนาดยาอิริโธรพอยอิตินและธาตุเหล็ก ระดับของธาตุเหล็กในเลือด และผลข้างเคียงต่างๆ

ผลการศึกษา: จำนวนครั้งของการใช้ตัวกรองซ้ำของกลุ่มที่ได้รับเฮพารินขนาดต่ำ น้อยกว่ากลุ่มที่ได้รับเฮพารินขนาดมาตรฐานอย่างมีนัยสำคัญทางสถิติ (17±4 vs. 13±5 ครั้ง, p<0.001) กลุ่มที่ได้รับเฮพารินขนาดต่ำมีค่า aPTT ที่ชั่วโมงที่ 2 (36±13 และ 70±36 วินาที, p<0.001) และ ชั่วโมงที่ 4 (31±10 และ 55±30 วินาที, P<0.001) หลังเริ่มต้นฟอกเลือด และ ค่า Kt/V (1.7±0.4 และ 1.9±0.4, p=0.001) ต่ำกว่ากลุ่มที่ได้รับเฮพารินขนาดมาตรฐานอย่างมีนัยสำคัญทางสถิติ ระดับฮีโมโกลบินของกลุ่มที่ได้รับเฮพารินขนาดต่ำ มีค่าสูงกว่ากลุ่มที่ได้รับเฮพารินขนาดมาตรฐานอย่างมีนัยสำคัญ ไม่พบความแตกต่างกันของขนาดยาอิริโธรพอยอิตินและธาตุเหล็ก และ ระดับของธาตุเหล็กในเลือด ในกลุ่มที่ได้รับเฮพารินขนาดมาตรฐานพบว่ามีเลือดออกเล็กน้อยที่เส้นฟอกเลือดจำนวน 2 ครั้ง นอกจากนี้ไม่พบความแตกต่างของผลข้างเคียงอื่นๆ ระหว่างทั้ง 2 กลุ่ม

สรุป: การใช้เฮพารินขนาดต่ำส่งผลให้สามารถใช้ตัวกรองซ้ำได้ในจำนวนครั้งที่ต่ำกว่าการใช้เฮพารินขนาดมาตรฐาน และ ยังพบผลในทางลบต่อความพอเพียงของการฟอกเลือด ดังนั้นจึงไม่ควรแนะนำให้ใช้เฮพารินขนาดต่ำเป็นยาต้านการแข็งตัวของเลือดสำหรับการฟอกเลือดด้วยเครื่องไตเทียม โดยเฉพาะในผู้ป่วยที่มีความเสี่ยงต่ำต่อภาวะเลือดออก

คำสำคัญ: เฮพาริน; การแข็งตัวของเลือด; ตัวกรอง; การฟอกไต; ไตวาย; การบำบัดทดแทนไต; การใช้ตัวกรองซ้ำ

Introduction

Heparin is one of the most commonly used anticoagulant agents to prevent clotting of hemodialysis (HD) circuit, dialyzer, and blood. Heparin is a sulfate polysaccharide that binds to antithrombin and inhibits thrombin and factor Xa. Heparin can reduce the incidence of blood clots but, on the other hand, higher dose of heparin can increase the risk of bleeding. Patients receiving

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maintenance HD are already at increased risk of bleeding due to impaired platelet function from accumulation of uremic toxins. Gastrointestinal bleeding, intracerebral hemorrhage and intra-abdominal bleeding are among the most common bleeding incidences in HD patients. Heparin can also inhibit lipoprotein lipase which normally breaks down triglycerides resulting in an elevation of triglycerides and increasing the risk of atherosclerosis. Heparin also suppresses angiotensin II receptors in the kidney causing a reduction in aldosterone resulting in an increase in serum potassium.[1]

Standard-dose heparin protocol (SDP) is the standard anticoagulant protocol of unfractionated heparin for maintenance HD. To alleviate the adverse effects of high dose heparin, low-dose heparin protocol (LDP) has been proposed.[2] The previous study comparing low-dose heparin (loading 5-10 units/pounds body weight and maintenance 10 units/pounds body weight/hour) with regional heparin revealed lower rate of bleeding complication with low-dose heparin (10% vs. 19%, $p< 0.05$)[3]. Another study using 50% reduction in the heparin dose showed no difference in the thrombosis rate compared with regional heparin. However, heparin-coated filter was used in this study.[4] The previous small study comparing SDP to LDP in maintenance HD revealed no difference in the number of dialyzer reuse. Lower erythropoietin dose and activated partial thromboplastin time (aPTT) were noted in the LDP group. However, the number of patients in each group was small making it difficult to draw a meaningful conclusion.[2]

Most countries continue to favor unfractionated heparin anticoagulation during HD procedure because of the ease of use and low cost. In Thailand, the standard loading and maintenance doses are 50 units/kg and 800-1,500 units/hour, respectively. Among patients with increased risk of bleeding, flushing with normal saline or regional citrate anticoagulation is recommended.[5] In the United States, typical loading and maintenance doses are 75–100 units/kg and 1000–1500 units/hour, respectively. In the Europe, the SDP consists of 50 units/kg loading with the maintenance rate of 800-1,500 units/hour, whereas the LDP consists of 10-25 units/kg loading with the maintenance rate of 500-1000 units/hour.[6] Dose reduction in patients at high risk of bleeding is a common practice in both the United States and Europe.

The present randomized crossover study was designed to examine the efficacy and safety of LDP compared with SDP in maintenance HD. The primary outcome was the difference in the number of dialyzer reuse and secondary outcomes were differences in aPTT, Kt/V, erythropoietin and iron requirements, iron parameters and adverse events.

Materials and Methods

Study Design and Setting

This is a randomized crossover trial in maintenance HD patients at Nawuti Somdet Ya Hospital, Bangkok, Thailand between April 2020 to January 2022. The study was approved by the Institutional Review Board of Police General Hospital and written informed consents were obtained from all participants.

Participants

Patients receiving outpatient in-center hemodialysis were screened for participation. The eligibility criteria were age ≥18 years, receiving HD 3 times/week and using unfractionated heparin as an anticoagulant. The exclusion criteria were: (1) receiving warfarin; (2) acute infection (body temperature ≥38.0°C); (3) congestive heart failure (swelling, shortness of breath, crepitations, volume overload on the chest x-ray); (4) hospitalization during the past month; (5) acute vascular event including coronary event, cerebrovascular accident and limb ischemia; (6) history of <10 times of dialyzer reuse; and (7) hepatitis or HIV infection.

Outcomes

The primary outcome was the difference in the number of dialyzer reuse. The dialyzer was replaced with the new one when the mean total cell volume (TCV) was <80% or when the reuse reached 20 times. Secondary outcomes were differences in TCV, aPTT, spKt/V, hemoglobin, erythropoietin and intravenous iron requirements, iron parameters, platelet count, serum potassium and triglycerides, and adverse events.

Estimation of the Sample Size

Based on the previous study, we hypothesized that the use of LDP would not influence the number of dialyzer reuse compared with SDP. The number of patients from that study was 100 per arm.[2]

Randomization and Crossover

The patients were randomized 1:1 to receive LDP (loading 15 units/kg and maintenance 500 units/hour) or SDP (loading 50 units/kg and maintenance 1,000 units/hour) until the TCV became <80% or the number of maximum reuse (20 times) was reached. The patient was then assigned a different regimen of heparin until the same endpoint was reached. (**Figure 1**)

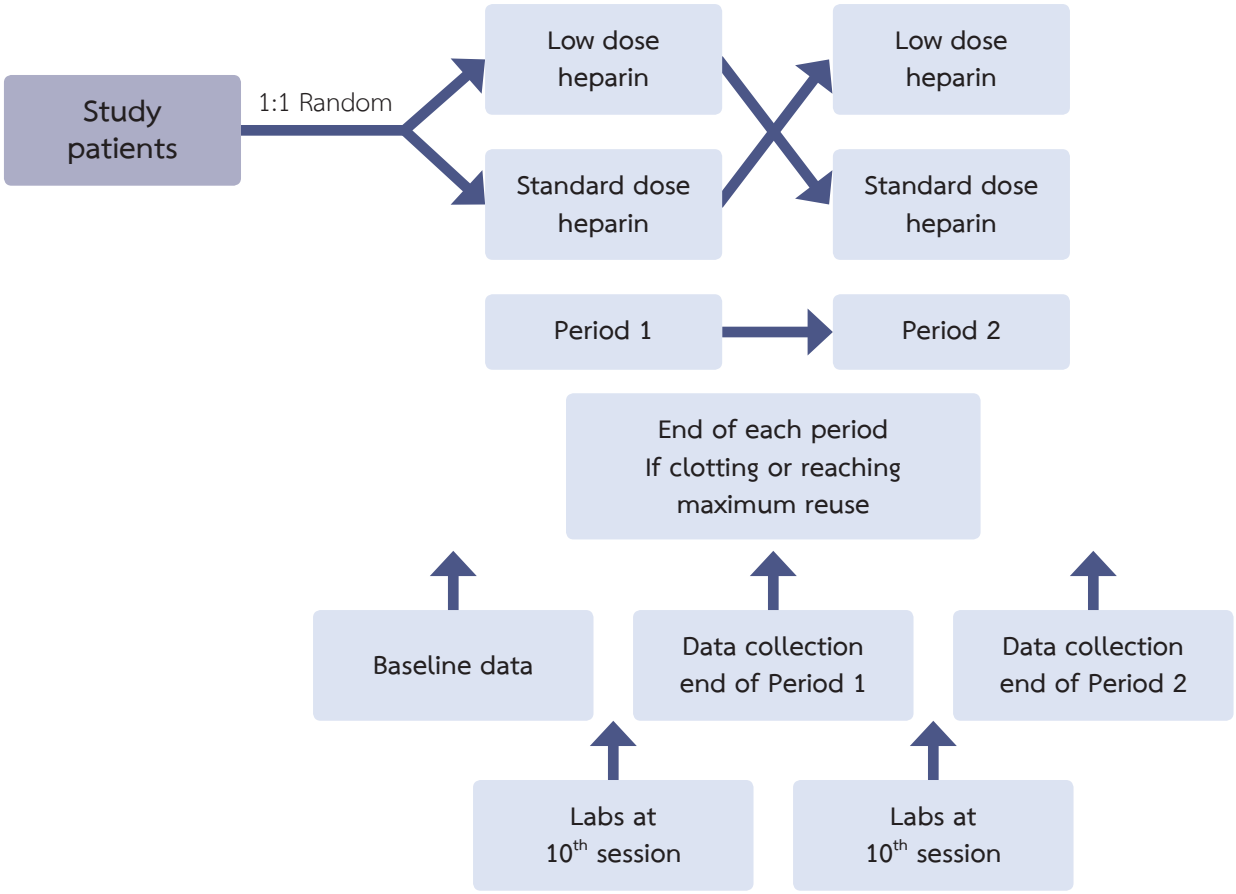

Figure 1. Study Diagram

Biochemical data

Baseline demographic data including age, sex, dry body weight, height, body mass index, dialysis vintage, underlying diseases, etiology of kidney failure, the use of antiplatelet agents, types of vascular access, blood flow, dialysate flow and ultrafiltration rates were recorded at baseline. Blood collection for laboratory tests were collected at the 10th HD session and at the end of the study. For aPTT test, blood was taken prior to the start of HD, at 2 hours into HD session and at the end of HD session. Bleeding events were recorded throughout the study period.

Statistical analysis

Data are presented as mean±standard deviation, median (interquartile range), frequency and proportion. Since this was a crossover study, the changes in primary and secondary outcomes were evaluated over a period of 3 months for each stage of the study. Differences between two groups were compared using Student's t-test, Wilcoxon signed-rank test, or Fisher's exact test. P<0.05 was considered statistically significant.

Results

One hundred patients were screened, and 75 patients were included in the final analysis (**Figure 2**). Baseline characteristics of all patients are shown in **Table 1**. The mean age was 55.9±14.8 years and the average body mass index was 23.1±4.6 kg/m^2. Forty three percent were females and 39% were diabetic. The median dialysis vintage was 5.6 years. Etiologies of end-stage kidney disease were hypertension 62.7% and diabetic nephropathy 33.4%. **Table 2** shows the type of vascular access, blood and dialysate flow rates and ultrafiltration rate for the LDP and SDP groups after randomization. The most common type of vascular access was arteriovenous fistula. Blood flow and dialysate flow rates and ultrafiltration rate were comparable between the two groups. **Table 3** shows the dose of unfractionated heparin in the LDP and SDP groups. The loading and maintenance doses were significantly lower in the LDP group compared with the SDP group.

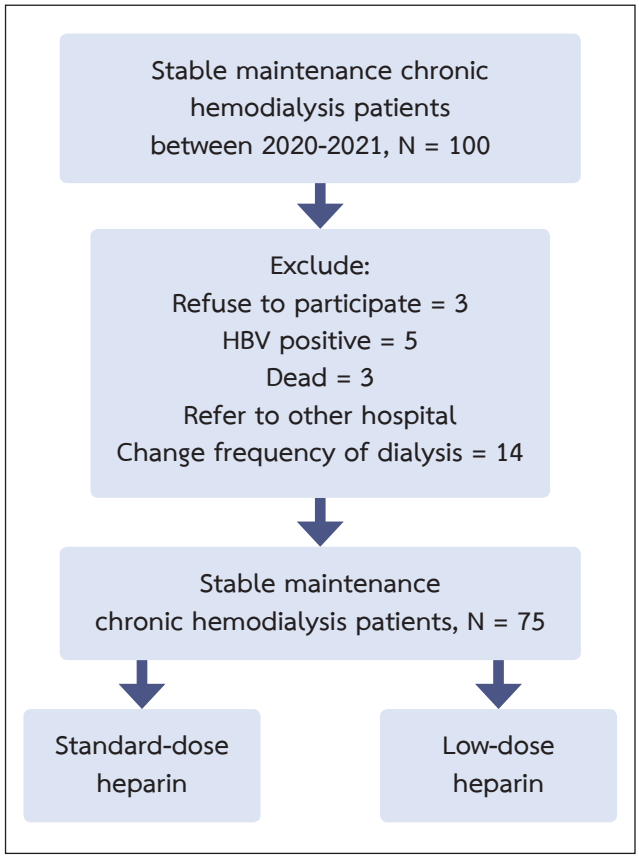

Figure 2 Study Flow Chart

Table 1. Baseline characteristics of all patients

Parameters	N=75
Age (years)	55.9±14.8
Female (n/%)	32 (42.7%)
Body weight (kg)	61.1±15.1
Height (cm)	162±8.8
Body mass index (kg/m^2)	23.1±4.6
Dialysis vintage (years)	5.6 (3.2,9)
Underlying diseases (n/%)	
Hypertension	73 (97.3%)
Diabetes mellitus	29 (38.7%)
Cardiovascular disease	15 (20%)
Others	28 (37%)
Etiology of kidney failure (n/%)	
Hypertension	47 (62.7%)
Diabetic nephropathy	25 (33.4%)
Others	3 (4%)
Use of antiplatelets and anticoagulants (n/%)	27 (36%)
Aspirin	20 (26.7%)
Aspirin and clopidogrel	4 (5.3%)
Aspirin and ticagrelor	1 (1.3%)
Apixaban	1 (1.3%)
Clopidogrel	1 (1.3%)

Table 2. Hemodialysis parameters

Parameters	Standard Dose	Low Dose
Double lumen catheter (n/%)	1 (1.3%)	1 (1.3%)
Arteriovenous fistula (n/%)	53 (70.7%)	53 (70.7%)
Arteriovenous graft (n/%)	8 (10.7%)	8 (10.7%)
Tunneled cuffed catheter (n/%)	13 (17.3%)	13 (17.3%)
Blood flow rate (mL/min)	354.7±60.5	353.3±61.7
Dialysate flow rate (mL/min)	524±81.9	520±75.3
Ultrafiltration rate (mL/hour)	684.7±220.1	695.3±225.4

Table 3. The amount of unfractionated heparin

Unfractionated Heparin	Standard Dose	Low Dose	P-value
Loading dose (units/kg)	46±7	13±3	<0.001
Total loading dose (units)	2773±768	817±307	<0.001
Maintenance dose (units/hour)	993±58	500±0	<0.001
Total maintenance dose (units)	2980±173	1500±0	<0.001
Total dose (units)	5753±844	2317±307	<0.001

The LDP group had significantly lower number of dialyzer reuse compared with the SDP group (13.3±5.3 vs. 17±4.4, p<0.001) (**Figure 3**). The TCV was also substantially lower in the LDP group. The aPTT values at 2 hours and 4 hours after the start of HD session were lower in the LDP group (**Table 4**). Lower spKt/V was observed in the LDP group. Hemoglobin was higher in the LDP group, but erythropoietin and iron requirements, transferrin saturation and serum ferritin were similar among the two groups. There were no differences in platelet count, serum triglyceride and potassium between the two groups (**Table 5**). Minor bleeding at vascular access site occurred only twice in the SDP group (0.2% vs. 0%, p=0.507). There was no incidence of major bleeding such as gastrointestinal bleeding or intracerebral hemorrhage in either group.

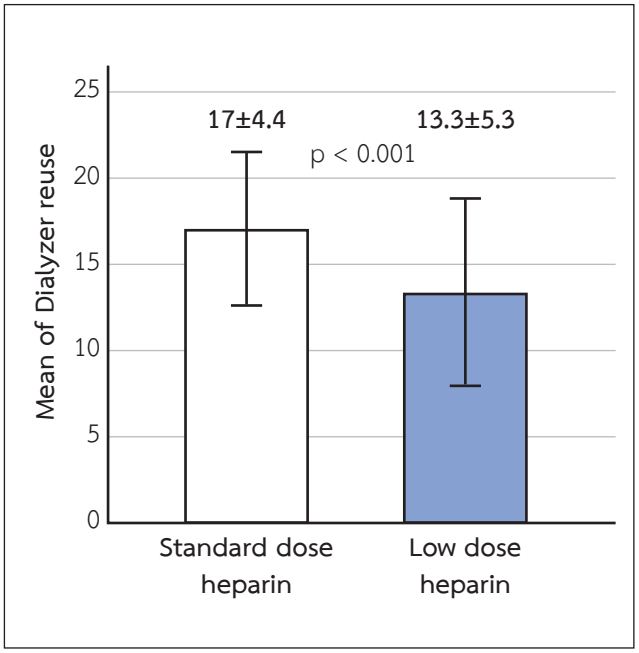

Figure 3. Number of dialyzer reuse

Table 4. Total cell volume and activated partial thromboplastin time after the start of hemodialysis session

Parameters	Standard Dose	Low Dose	P-value
TCV (ml)	95.2±15.5	78.3±19	<0.001
aPTT (seconds)			
0 hour	32.3±12.6	31.8±17.8	0.8724
2 hours	69.8±35.9	36.3±12.7	<0.001
4 hours	54.5±29.8	31.3±10	<0.001

TCV, total cell volume; aPTT, activated partial thromboplastin time

Table 5. Dialysis adequacy, erythropoietin and iron requirements and laboratory data

Parameters	Standard Dose	Low Dose	P-value
spKt /V	1.9±0.4	1.7±0.4	0.001
Hemoglobin (g/dL)	9.3±1.3	9.7±1.3	0.015
Erythropoietin (units/week)	9324±3445	9149±3455	0.17
Intravenous iron (mg/month)	428.6±221.7	371.4±239.0	0.414
Transferrin saturation (%)	31.2±13.1	31.2±13.7	0.99
Ferritin (ng/mL)	258.1 (139.7,427.4)	318.8 (121.3,450.5)	0.095
Platelets (cells x 1000/μL)	192.6±59.5	191.7±64.9	0.818
Serum triglyceride (mg/dL)	118 (82,160)	115 (74,167)	0.798
Serum potassium (mmol/L)	4.2±0.5	4.2±0.6	0.628

Discussion

The main findings of the present study included LDP significantly reduced the number of dialyzer reuse compared with SDP. This was associated with lower TCV and spKT/V in the LDP group. Apart from lower hemoglobin in the SDP group, other parameters including erythropoietin and intravenous iron requirements, iron parameters, platelet count serum triglyceride and potassium were comparable between the two groups. Minor bleeding at vascular access site occurred twice in the SDP group.

The reduced number of dialyzer reuse in the LDP group was likely due to an increase in minute clotting within the dialyzer. This was supported by lower aPTT values at 2 hours and 4 hours after the start of HD in the LDP group. The previous study has demonstrated the association between higher aPTT and decreased likelihood of blood clots in the dialyzer.[7] The average value of TCV was also significantly lower in the LDP group which reflected the continued reduction in the effective dialyzer volume due to repeated clotting. This resulted in lower spKt/V in the LDP group.

The average hemoglobin in the LDP group was substantially higher compared with the SDP group. Bleeding events, erythropoietin and intravenous iron requirements and iron parameters were similar between the two groups and could not explain the difference in hemoglobin. It is possible that minute bleeding at vascular access site might occurred more frequently in the SDP group. This small amount of bleeding might be considered trivial at the time but the cumulative effect over several HD sessions could result in a decrease in hemoglobin in the SDP group.

Other side effects of high dose heparin including thrombocytopenia, increased serum triglyceride and potassium were not different between the LDP and SDP groups confirming the safety of SDP in maintenance HD. The strength of this study is the study design which is a randomized crossover trial. The present study is limited by small number of patients and the use of surrogate outcomes.

In conclusion, LDP resulted in a lower number of dialyzer reuse compared with SDP. This was associated with reduced TCV and dialysis adequacy in the LDP group. LDP offered no advantage in terms of side effects compared with SDP. Therefore, LDP should not be recommended in prevention of dialyzer clotting in maintenance HD patients with low risk of bleeding.

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