



# Assessment of the Administration of Low Molecular Weight Heparin for Hemodialysis Anticoagulation in Comparison to Standard Unfractionated Heparin

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## Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

## Article Information

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## ABSTRACT

**Background and Aim of Study:** The use of Low-molecular-weight heparin (LMWH) for hemodialysis anticoagulation has been proposed as effective and safe for hemodialysis (HD) anticoagulation as standard unfractionated heparin (UFH). The aim of our study was to assess the use of LMWH for hemodialysis anticoagulation in comparison to UFH, including hemorrhagic events and clotting of the extracorporeal dialysis circuit and their effect on lipids profile.

**Methods:** This prospective, randomized study conducted on 44 patients (31 males, 13 females; mean age 53.7.9±14.2 years) with end-stage renal disease on regular hemodialysis. The hemodialysis patients were subjected to UFH and followed prospectively for 16 weeks (48 dialyses sessions) and the same patients were subjected to LMWH (enoxaparin sodium; 40 mg) for a further 16 weeks, clotting of the extracorporeal dialysis circuit and hemorrhagic events were evaluated by visual inspection of the air trap, blood lines and dialyzers and the time required for arterio-venous fistula compression. Kt/V was calculated to determine whether UFH or LMWH had any effect on the adequacy of dialysis and lipid profile were measured at the end of each arm of the study to determine whether UFH or LMWH had any effect on the lipid profile levels.

**Results:** The present study showed that, compared with UFH, the effect of LMWH (enoxaparin

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sodium) on the number of hemorrhagic events (relative risk, 1.3; 95% CI: 0.317 - 5.613; P=1.000) or clotting of the extracorporeal dialysis circuit (relative risk, 0.75; 95% CI: 0.284 - 1.984; P=1.000) was not significant. There was no significant difference in Kt/V between the UFH arm (1.4±0.4) and LMWH (enoxaparin sodium) arm (1.5±1.2; p=0.6). Also there was no significant differences in serum total Cholesterol, LDL, HDL and TGs between the UFH arm and LMWH (enoxaparin sodium arm).

**Conclusion:** LMWH (Enoxaparin sodium) should be considered as effective and safe as unfractionated heparin in hemodialysis anticoagulation. But currently direct costs are about 26% more. So we recommend, the use of UFH for its low cost.

*Keywords: Anticoagulation; hemodialysis; heparin; enoxaparin.*

## 1. INTRODUCTION

Many studies have shown that Low molecular weight heparins (LMWH), which are a fractionated heparin, are effective as unfractionated heparin (UFH), commonly used for the prevention and treatment of many thromboembolic diseases [1]. There are no need for routine laboratory monitoring of the anticoagulant effect of LMWH, allowing many patients with thromboembolic diseases to be treated as outpatients without need for hospital admission. LMWH has lower incidences of heparin-induced thrombocytopenia and osteoporosis than UFH [1,2].

LMWH inhibits factor Xa, whereas UFH inhibits both factor Xa and thrombin equally. Therefore, the anticoagulant effects of LMWH are monitored by measuring the ability of plasma from patients who are treated with LMWH to inhibit factor Xa; the resultant assay is known as an anti-Xa heparin level. The anti-Xa heparin level reflects the amount of LMWH present in the blood and the degree of anticoagulation. Although the minimal therapeutic anti-Xa level has not been established, a conservative therapeutic range measured 4 h after a subcutaneous dose is 0.6 to 1.0 IU/ml for twice-daily administration and 1.0 to 2.0 IU/ml for once-daily administration [1,3].

LMWH are dependent on renal clearance, whereas UFH is cleared through hepatic and renal mechanisms. Thus, the patients with renal failure are at increased risk for bleeding as a result of impaired clearance of LMWH and prolonged anticoagulant effects. Many observational studies and randomized trial data report increased bleeding using LMWH in patients with renal impairment compared with those without renal impairment [1,4-7]. Moreover, LMWHs are more expensive in comparison to UFH [8].

LMWHs do not bind to plasma proteins, platelets, and endothelium and do not stimulate plasma lipase activity as much as UFH, therefore, LMWHs have high bioavailability, and less complications as UFH [9,10].

In patients with ESRD on maintenance hemodialysis, LMWHs are not commonly used for therapeutic anticoagulation in these patients, but they can be used to prevent thrombosis of extracorporeal dialysis circuit. LMWH are not cleared from the plasma during hemodialysis [1,11] or continuous veno-venous hemofiltration [1,12]. Thus, LMWHs have a risk of plasma accumulation and bleeding when used regularly for patients with ESRD on maintenance hemodialysis. Many randomized controlled trials have assessed the use of LMWH for hemodialysis anticoagulation to prevent clotting of the dialysis circuit and are used for this indication in many countries [1].

The aim of our study was to assess the use of LMWH for hemodialysis anticoagulation in comparison to UFH, including the risk of bleeding and clotting of the extracorporeal dialysis circuit and their effect on lipids profile.

## 2. PATIENTS AND METHODS

Our prospective, randomized, cross-over study, included 44 adult patients (31 males, 13 females; mean age 53.7.9±14.2 years) with ESRD on regular hemodialysis, Theodor Bilharz research Institute (TBRI), Cairo, Egypt. A written Informed consent was obtained from all patients included in this study.

Our patients received maintenance hemodialysis three sessions per week for 4 hrs per session at blood flow rates of 300-350 ml/min. Polysulfone membrane dialyzers were the most common used dialyzers. In all patients, the vascular access was via arteriovenous fistula. Patients

with known bleeding disorders or on maintenance anticoagulant or antiplatelet therapy (e.g. warfarin, aspirin) were excluded from the study.

During the period of the study, the patients were received their usual medications including lipid-lowering therapy and antihypertensive medications. When necessary the patients were received recombinant erythropoietin to maintain haemoglobin level of 11–12 g/dl.

Patients were randomly subjected to receive standard UFH and followed prospectively for 16 weeks (48 dialysis sessions). The same patients were then subjected to receive LMWH (enoxaparin sodium; 40 mg and followed prospectively for a further 16 weeks (48 dialysis sessions).

A bolus dose (50 IU/kg body weight) of UFH (5000 IU/ml) was administered into the pre-dialyzer arterial line of the extracorporeal blood circuit, followed by a maintenance dose of 1000 IU UFH per hour. UFH administration was discontinued 1 h before the end of HD session. A single bolus dose of LMWH (enoxaparin sodium, 40 mg) was administered into the pre-dialyzer arterial line of the extracorporeal blood circuit, 2-3 min before the dialysis session. Clotting of extracorporeal blood circuit was assessed by visual inspection of the air bubble trap every 30 min and the blood lines and the dialyzer after the session.

At the end of dialysis session, the blood in extracorporeal blood circuit had been returned to the patient by flushing the dialyzer and blood lines with normal saline. The degree of clot formation in extracorporeal blood circuit (blood lines and dialyzer) was assessed as score from 0-3-point scale, with 0 scale indicating no clot formation and 3 scale indicating severe clotting or total occlusion of extracorporeal blood circuit. Bleeding or thrombosis, during and between dialysis sessions was also assessed.

Bleeding also evaluated by the time required for arterio-venous fistula compression for UFH and LMWH arm.

Regarding bleeding episodes were assessed as mild, moderate, and severe. Kt/V was calculated per month using Daugirdas formula [13], to determine whether LMWH or UFH had any effect on the adequacy of dialysis.

At the end of each arm of the study, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TG) were measured to determine whether LMWH or UFH had any effect on the lipid profile levels.

## 2.1 Statistical Analysis

Quantitative data were analysed as Mean  $\pm$  Standard Deviation or percentage. The distribution of variables was evaluated by One-Sample Kolmogorov-Smirnov Test, and the differences between variables were determined using paired t-test for parametric data or Wilcoxon Signed Ranks Test for non-parametric data as appropriate. The analysis was performed using Statistical Analysis System, version 6.03, on an IBM at personal computer and MedCalc for windows (version 12.7.5). P value <0.05 was considered significant.

## 3. RESULTS

The most causes of ESRD were glomerulonephritis, diabetes mellitus and hypertension. Demographic characteristics of the studied patients are shown in Table 1.

With UFH, clotting of the extracorporeal dialysis circuit was noted in 8 of the 44 patients (18.2%) (Fig. 1) and bleeding occurred in 3 of the 44 patients (6.1%) (Fig. 2).

With LMWH (enoxaparin sodium, 40 mg), clotting of the extracorporeal dialysis circuit was noted in 6 of the 44 patients (13.6%) (Fig. 1) and bleeding occurred in 4 of the 44 patients (9.1%) (Fig. 2).

Compared with UFH, the effect of LMWH (enoxaparin sodium) on the number of hemorrhagic events (relative risk, 1.3; 95% CI: 0.317 - 5.613;  $P=1.000$ ) or extracorporeal dialysis circuit thrombosis (relative risk, 0.75; 95% CI: 0.284 - 1.984;  $P=1.000$ ) was not significant.

None of the episodes of clotting of the extracorporeal dialysis circuit was severe enough to warrant change of the dialyzer or blood lines. None of the bleeding episodes on LMWH (enoxaparin sodium) required blood transfusion and the bleeding could be controlled by venous compression at the site of arterio-venous fistula.

Compared with UFH, bleedings evaluated by the time required for arterio-venous fistula compression (mean difference, -0.65; 95% CI: -1.55 - 0.82) was not significant.

There was no significant difference in Kt/V between the UFH arm (1.4±0.4) and LMWH (enoxaparin sodium arm (1.5±1.2; p=0.6) (Table 2).

Also there was no significant differences in serum total Cholesterol, LDL, HDL and TGs between the UFH arm and LMWH (enoxaparin sodium arm (Table 2).

By calculation the cost of both UFH and LMWH anticoagulants, currently direct costs of LMWH are about 26% more than UFH.

**4. DISCUSSION**

The present study showed that, compared with UFH, the effect of LMWH (enoxaparin sodium) on the number of hemorrhagic events (relative risk, 1.3; 95% CI: 0.317 - 5.613; P= 1.000) or extracorporeal circuit thrombosis (relative risk,

0.75; 95% CI: 0.284 - 1.984; P=1.000) was not significant.

Our results are consistent with a Meta-Analysis carried out by LIM et al. [1], it was shown that the number of hemorrhagic events, bleedings evaluated by the time required for arterio-venous fistula compression or extracorporeal circuit thrombosis are not significantly affected by LMWHs (relative risk, 1.15; 95% CI, 0.70 to 1.91) in comparison to UFH. Compared with UFH, LMWH appears to be as safe (in terms of bleeding complications) and as effective (in preventing extracorporeal circuit thrombosis). However, until larger, more exact randomized trials are conducted no strong conclusion can be made from these trials assessing anticoagulation for patients who undergo hemodialysis [1].

Aggarwal et al. [14], showed that in contrast to UFH, the use of LMWH (enoxaparin sodium) as anticoagulant, during hemodialysis is associated with less platelet reactivity Therefore, patients with ESRD treated with hemodialysis may benefit from LMWH (enoxaparin sodium) administration, as it decreases the risk of cardiac events [14].

**Table 1. Demographic characteristics of the studied patients**

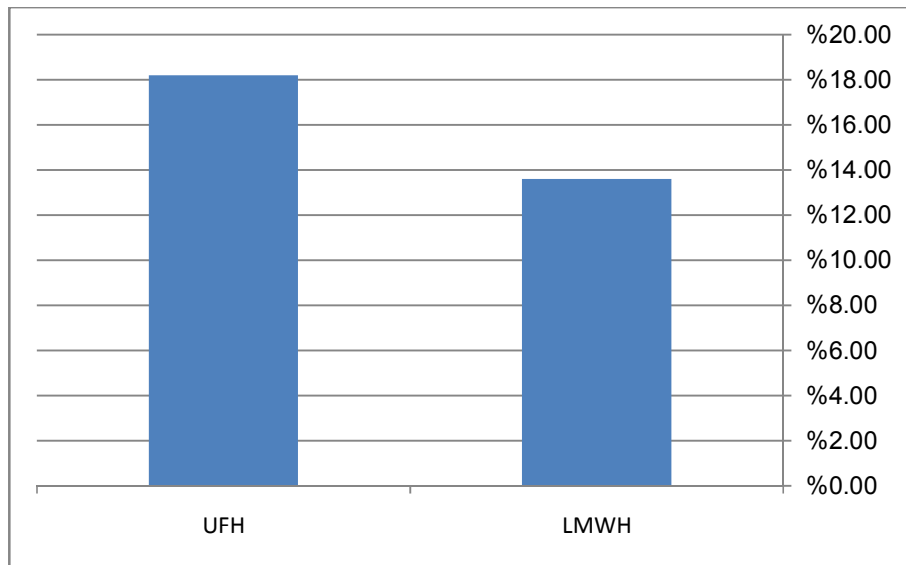
Variable	Studied patients (No.44)
Age (years)	53.7.9±14.2 (23-67)
Sex	
Male	31(70.45%)
Female	13(29.55%)
BMI (kg/m <sup>2</sup> )	23±3.4 (18.2-28.6)
Duration on dialysis (month)	14.6±3.8 (2-54)
Aetiology of ESRD	DM (12 patients) Hypertension (10 patients) Glomerulonephritis (9 patients) Lupus nephritis (4 patients) Analgesic nephropathy (2 patients) APKD (2 patients) Unknknown (5 patients)

*ESRD=end-stage renal disease. DM=diabetes mellitus. APKD=adult polycystic kidney disease*

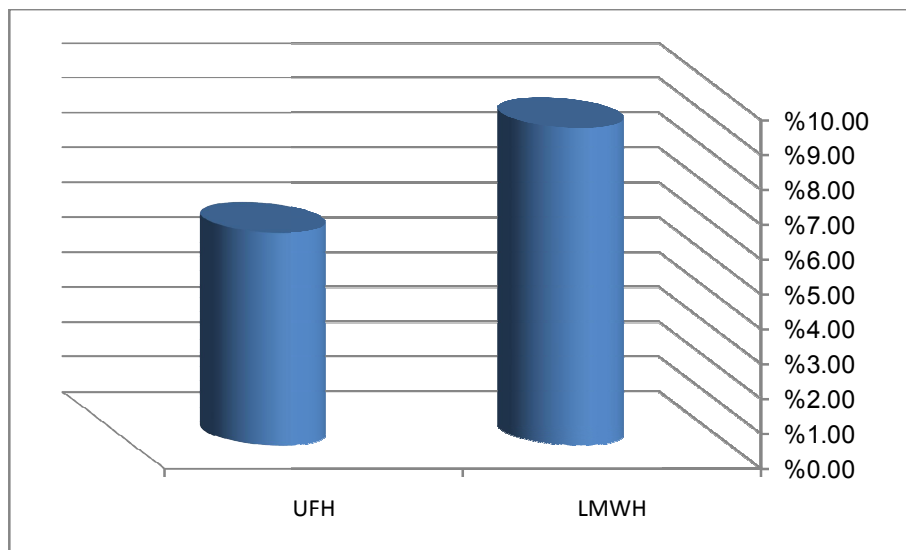
**Table 2. Lipid profile and KT/V, after 16 weeks of UFH and LMWH (enoxaparin sodium)**

Variable	After unfractionated heparin	After enoxaparin sodium	P value
Lipid profile			
Total cholesterol (mg/dl)	132.7±26.54	136.3±27.8	P=0.53
HDL-cholesterol (mg/dl)	35.7±9.8	34.7±5.2	P=0.55
TGs	138.3±58.6	143.2±56.8	P=0.6
KT/V	1.4±0.4	1.5±1.2	P=0.6

*HDL-cholesterol=high denisty lipoprotein-cholesterol. TGs=triglycerides*



**Fig. 1. Percentage of clotting in patients receiving low molecular weight heparin (LMWH) and unfractionated heparin (UFH)**



**Fig. 2. Percentage of bleeding in patients receiving low molecular weight heparin (LMWH) and unfractionated heparin (UFH)**

Lim et al. [15], in another Meta-Analysis of 11 Randomized Trials demonstrated that in patients with severe renal impairment (GFR  $\leq 30$  mL/min) compared with those without (GFR  $>30$  mL/min), the use of standard therapeutic-dose LMWH (enoxaparin sodium) leads to higher levels of anti-Xa. Consequently there is a 2 to 3 fold increase in the risk of major hemorrhagic events [15].

LIM found that, compared with UFH, the effect of LMWH on the number of hemorrhagic events (relative risk, 0.96; 95% CI: 0.27 - 3.43), bleedings assessed by the time required for vascular access compression (mean difference, - 0.87; 95% CI: -2.75 - 1.02), or extracorporeal circuit thrombosis (relative risk, 1.15; 95% CI: 0.70 - 1.91) was not significant. In comparison to UFH, LMWH has the same amount of efficacy in preventing extracorporeal circuit thrombosis and

it is as safe in terms of bleeding complications. However, drawing strong conclusions from these trials, requires more rigorous randomized trials [15].

In a study Guillet et al. [16], suggest that in hemodialysis patients there is an increased risk of bleeding up to 10 hour after the injection of LMWH enoxaparin sodium.

As reported by Saltissi et al. [17], early in the use of the enoxaparin sodium minor interdialytic Hemorrhage (none requiring clinical intervention) increased among patients, which might be unnoticed until after four to eight dialyses. There was no difference in the frequency of bleeding or thrombosis between the groups [17].

In a review article, Schmid et al. [18], proposed a detailed approach for LMWH administration in patients with severe renal impairment. In brief, this approach included: evaluation of the patient's renal function, imminent interventions, and general bleeding risk before prescribing LMWH. LMWH has higher efficacy and lower bleeding risks in general. In unstable patients, or patients who have a high tendency for Hemorrhage, IV UFH is preferred to SC LMWH, as IV UFH, has a shorter half-life time, and can be quickly antagonized.

Schmid Concluded that though LMWH might be considered in severe renal insufficiency patients, caution choice and careful monitoring of these patients are necessary [18].

As laboratory monitoring of LMWH is not needed and the ease of administration of LMWH (single bolus pre-dialysis) are of its advantages [8,17,19,20,21].

UFH besides anticoagulation properties, releases lipoprotein lipase from its active site at the capillary endothelial surface [17].

In our study, there was no significant differences in serum total Cholesterol, LDL, HDL and TGs after using either anticoagulant and also there was no significant difference in KT/V values between the groups ( $1.5 \pm 1.2$  for LMWH (enoxaparin sodium) vs  $1.4 \pm 0.4$  for heparin;  $P=0.6$ ).

Al-Saran [22] reported that LMWH (tinzaparin sodium) resulted in less frequent dialyzer and air-trap clotting than UFH, and there was no change in serum lipid profile of the patients, over 24

weeks. The dialysis single pool Kt/V was improved after 6 months of LMWH (tinzaparin sodium) use ( $1.40 \pm 0.28$  for tinzaparin versus  $1.23 \pm 0.28$  for heparin) [23]. Saltissi observed no effects on lipids over 3 months too [17].

Spaia et al. [23], found significantly lower HDL and higher triglyceride concentrations after 33 months of the LMWH treatment.

Sabry et al. [24], reported no statistically significant differences in serum lipids (cholesterol, LDL, triglyceride and HDL), Hb, white blood cells count and platelet count after changing from UFH to tinzaparin sodium.

## 5. CONCLUSION

LMWH (enoxaparin sodium) should be considered as effective and safe as UFH in hemodialysis anticoagulation. But currently direct costs are about 26% more. So we recommend, the use of UFH for its low cost.

## ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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