Effect of Switching Unfractionated Heparin to Low-Molecular-Weight Heparin on Serum Potassium in Hemodialysis Patients

Shahrokh Ezzatzadegan Jahromi,[1] Mohammad Saleh Mahmoodi,[2] Fatemeh Behroozi,[3] Jamshid Roozbeh,[1] Fatemeh Emamghoreishi[4]

[1]Shiraz Nephrology Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Internal Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Jahrom University of Medical Sciences, Jahrom, Iran
[4]Department of Pediatrics, Jahrom University of Medical Sciences, Jahrom, Iran

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Introduction. Unfractionated (UF) heparin is the most common anticoagulant used during hemodialysis. Failure of the kidneys to excrete potassium as well as heparin-induced reduction of aldosterone synthesis put hemodialysis patients at risk of hyperkalemia. It has not yet been clearly known whether hyperkalemia is also induced by low-molecular-weight (LMW) heparins. This study aimed to evaluate the effect of switching UF heparin to LMW heparin enoxaparin, as an anticoagulant during hemodialysis, on serum potassium level in patients on hemodialysis.

Material and Methods. In two hemodialysis units, 58 patients were randomly assigned into two groups, to receive two different anticoagulation protocols for 3 weeks; one group continued to receive their routine dose of UF heparin, 5000 units, and the other received enoxaparin, 0.5 mg/kg, at the beginning of each hemodialysis session.

Results. While there was no significant difference between baseline blood measurements of the two groups in terms of kidney function tests and electrolytes, following 3 weeks of the study, the mean serum potassium level decreased from 4.9 ± 0.8 mEq/L to 4.5 ± 0.5 mEq/L in the LMW heparin group (P = .001); however, there was no change in the mean serum potassium level in those who continued to receive their usual dose of UF heparin. In a subgroup analysis, diabetic patients in the enoxaparin group did not experience significant reduction in serum potassium levels.

Conclusions. Our study revealed the role of LMW heparins as a potential alternative to UF heparins in the hemodialysis patients with hyperkalemia.

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INTRODUCTION

Prevention of clotting in the extracorporeal blood flow is one of the basic principles of a successful hemodialysis. Unfractionated (UF) heparin is the most common anticoagulant agent used during hemodialysis although it has been replaced by low-molecular-weight (LMW) heparins in European countries.[1] Administration of UF heparin is associated with some side effects. There are a minority of hemodialysis patients who have manifestations of these complications. While bleeding is the most serious side effect of all anticoagulant agents, there are additional risks attributed to the use of UF heparin such as heparin

induced thrombocytopenia, osteoporosis, hair loss, abnormalities in lipid profile, and suppression of aldosterone synthesis.[2]

Compared to UF heparin, LMW heparins have some advantages when used for anticoagulation during hemodialysis, including lower risk of thrombocytopenia, less impact on lipid profile and bone metabolism, and lower risk of hair loss.[2,3] Furthermore, with less binding to the endothelium, LMW heparins have a higher bioavailability. On the other hand, due to longer biological half-life of LMW heparins, it could be administrated as a single dose, whereas there is no risk of drug accumulation in thrice-weekly administration for hemodialysis despite reduction of renal excretion.[4]

Failure of the kidneys to excrete potassium as well as heparin-induced reduction of aldosterone synthesis puts the hemodialysis patients at risk of life-threatening hyperkalemia.[5] Additionally, because hemodialysis patients are susceptible to hyperkalemia, hypoaldosteronism might lead to a higher risk of potassium-related life threatening complications. It has not yet been clearly known whether hyperkalemia is also induced by LMW heparins or not; however, some studies have shown that significant inhibition of mineralocorticoid production requires high doses of LMW heparins.[6-10]

As data regarding the role of LMW heparins in aldosterone suppression and inducing hyperkalemia is scarce in hemodialysis patients, we performed this study in order to evaluate the effect of switching UF heparin to LMW heparin *enoxaparin*, as an anticoagulant during hemodialysis, on the serum level of potassium in patients undergoing chronic hemodialysis.

MATERIALS AND METHODS

Participants

This was a randomized clinical trial performed at two hemodialysis units, hemodialysis unit of Shahid Faghihi Hospital in Shiraz, Iran, and hemodialysis unit of Motahari Hospital in Jahrom, Iran, which are affiliated with Shiraz University of Medical Sciences and Jahrom University of Medical Sciences, respectively. We included the patients who were on regular 12-hour per week hemodialysis for at least 3 months. We excluded all the patients with a history of major recent bleeding episodes, those with abnormalities in coagulation profiles, those with a history of oral anticoagulation consumption, and those who received diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroid anti-inflammatory drugs. The study protocol was approved by the ethics committees of Shiraz University of Medical Sciences and Jahrom University of Medical Sciences.

Study Protocol

A total of 58 patients eligible for the study were randomly assigned into 2 groups, 29 patients in each, to receive 2 different anticoagulation protocols for 3 weeks. Those who were assigned to UF heparin group continued to receive their usual dose of UF heparin, 5000 units at the beginning of each hemodialysis session. For LMW heparin group, the routine UF heparin was discontinued and 0.5 mg/kg (50 IU/kg) of enoxaparin)Clexane, Sanofi Aventis(was given at the beginning of each hemodialysis session. Hemodialysis was performed using bicarbonate dialysate for 4 hours, 3 times a week, using a similar polysulfone dialysis membrane (Fresenius, Germany) with a dialysate potassium concentration of 2 mEq/L.

Sera of blood samples collected at the initiation of the study were immediately frozen and serum levels of urea nitrogen, creatinine, phosphate, and potassium were measured at the same time with the samples taken at the end of the study.

Statistical Analysis

All statistical analyses were performed with the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). The chi-square test was used to compare the nonparametric data and proportions between the groups. Parametric data were compared between the groups using the independent *t* test, and changes within groups were compared with the paired *t* test. Data were reported as mean ± standard deviation. A two-sided *P* value less than .05 was considered significant.

RESULTS

All of the patients completed the study and no bleeding or extracorporeal circuit thrombosis was reported. A total of 58 patients were included, 29 patients in each group, with similar sex distributions (19 men and 10 women in each group). The mean age values of the patients receiving UF heparin and

LMW heparin were 52.8 ± 15 years and 55.6 ± 17 years, respectively (P = .51; Table 1). The number of diabetic patients was 6 (20%) in the UF heparin and 14 (48%) in the LMW heparin group (P = .03). As shown in Table 1, there were no significant differences between baseline values of the two groups in terms of blood urea nitrogen, serum creatinine, and serum phasphate levels. Comparison of these variables between the two groups revealed no significant difference following 3 weeks of UF heparin and LMW heparin either (Table 2).

Baseline serum potassium levels were 4.9 ± 0.7 mEq/L and 4.9 ± 0.8 mEq/L in the UF and LMW heparin groups respectively (P = .82). Following 3 weeks of the study, the mean serum potassium level decreased significantly to 4.5 ± 0.5 mEq/L in the LMW heparin group (P = .001); however, there was no change in the mean serum potassium level in those who continued to receive their usual dose of UF heparin (from 4.9 ± 0.75 mEq/L to 4.9 ± 0.74 mEq/L, P = .60; Table 2).

As shown in Table 3, while diabetic patients in the UF heparin group had comparable serum potassium levels at the end of the study with the baseline values (from 4.8 ± 0.5 mEq/L to 4.8 ± 0.5 mEq/L, P > .99), patients in LMW heparin group experienced a nonsignificant reduction in serum potassium levels (from 4.7 ± 0.6 mEq/L to 4.4 ± 0.5 mEq/L, P = .06). Baseline levels of blood urea nitrogen, serum creatinine, and serum phasphate were not significantly different from the values at the end of the study in both groups with diabetes mellitus.

Table 1. Demographic Characteristics and Baseline Serum Values of Hemodialysis Patients

Parameter	Unfractionated Heparin Group (n = 29)	Enoxaparin Group (n = 29)	*P*
Mean age, y	52.8 ± 15.0	55.6 ± 17.0	.51
Sex			
Female	10	10	
Male	19	19	> .99
Diabetes mellitus	6 (20%)	14 (48%)	.02
Mean serum values			
Blood urea nitrogen, mg/dL	45.9 ± 22.9	48.9 ± 25.7	.64
Creatinine, mg/dL	6.5 ± 3.8	5.8 ± 3.6	.51
Phosphate, mg/dL	4.1 ± 1.6	4.3 ± 1.4	.52
Potassium, mEq/L	4.9 ± 0.7	4.9 ± 0.8	.82

DISCUSSION

It has been shown that UF heparin suppresses the aldosterone synthesis and might cause hyperkalemia in those who receive long-term UF heparin particularly in patients undergoing regular hemodialysis.[1,5,11] The precise mechanism of heparin-induced hyperkalemia is not yet clear; however, experimental studies in rat have shown that the number and the affinity of adrenal angiotensin II receptors are reduced, leading to decreased binding of angiotensin.[12] This phenomenon is limited to the zona glomerulosa and other parts of the gland are not involved in the pathogenesis of aldosterone suppression following treatment with UF heparin.[13]

Table 2. Kidney Function Measurements and Electrolytes Before and After 3 Weeks of Treatment With Unfractionated Heparin and Enoxaparin

	Unfractionated Heparin Group (n = 29)			Enoxaparin Group (n = 29)		
Mean Serum Values	Baseline	After 3 Weeks	*P*	Baseline	After 3 Weeks	*P*
Blood urea nitrogen, mg/dL	45.9 ± 22.9	47.0 ± 22.3	.55	48.9 ± 25.7	48.9 ± 27.5	.98
Creatinine, mg/dL	6.5 ± 3.8	6.4 ± 3.6	.63	5.8 ± 3.6	5.5 ± 3.4	.13
Phosphate, mg/dL	4.1 ± 1.6	4.3 ± 1.5	.14	4.3 ± 1.4	4.7 ± 2.0	.13
Potassium, mEq/L	4.9 ± 0.7	4.9 ± 0.7	.60	4.9 ± 0.8	4.5 ± 0.5	.001

Table 3. Kidney Function Measurements and Electrolytes Before and After 3 Weeks of Treatment With Unfractionated Heparin and Enoxaparin in Diabetic Patients.

	Unfractionated Heparin Group (n = 6)			Enoxaparin Group (n = 14)		
Mean Serum Values	Baseline	After 3 Weeks	*P*	Baseline	After 3 Weeks	*P*
Blood urea nitrogen, mg/dL	37.5 ± 6.8	36.6 ± 5.9	.55	46.5 ± 24.7	43.7 ± 26.7	.20
Creatinine, mg/dL	4.4 ± 1.5	4.5 ± 1.4	.12	5.6 ± 3.6	5.1 ± 3.3	.08
Phosphate, mg/dL	3.5 ± 0.7	3.4 ± 0.6	.68	3.8 ± 1.1	3.9 ± 1.6	.87
Potassium, mEq/L	4.8 ± 0.5	4.8 ± 0.5	> .99	4.7 ± 0.6	4.4 ± 0.5	.057

In individuals with intact kidney function, suppression of aldosterone and subsequent sodium loss and potassium retention starts shortly after initiation of heparin therapy and reaches its peak after 3 to 5 days. This effect is dose dependent, reversible, and not related to either anticoagulant effect or administration route.[1,14] Although hyperkalemia is often reported to occur after treatment with a high dose of UF heparin, occurrence with low-dose heparin administration (5000 units subcutaneously, twice a day for 10 days) has also been reported in healthy subjects with normal kidney function.[1]

Reduction of heparin elimination by the kidneys along with decreased potassium excretion in patients with end-stage renal disease could put these patients at risk of hyperkalemia even with low doses of UF heparin used as anticoagulation during hemodialysis.[15] While serious hyperkalemia has been reported in 10% of hemodialysis patients, hyperkalemia is the cause of 3% to 5% of deaths in end-stage renal disease patients.[16,17] The other well-known anticoagulant agents, LMW heparins, are supported by ample evidence form several studies to be used during hemodialysis with similar efficacy and safety compared to UF heparin.[2,18-20] Single bolus administration with recommended dosages of 0.4 mg/kg to 1 mg/kg is one of the advantages of LMW heparins over UF heparins.[4,15,19,21] It should be mentioned that one of the main barriers of extensive use of LMW heparins is higher costs relative to UF heparins.

It is not yet fully known whether suppression of aldosterone synthesis and subsequent hyperkalemia also occurs with LMW heparins or not. The results of the studies have been influenced by whether LMW heparins were used as treatment or as prophylaxis for venous thrombosis. Prophylactic doses of LMW heparin enoxaparin was shown to have no significant effect on serum potassium level after 4 days of administration in the study done by Potti and colleagues, which is in agreement with similar studies.[8,22] When used with therapeutic dosages, LMW heparins have been shown to increase serum potassium level even with 3 days of administration.[9,10] While diabetes mellitus was found to be an independent risk factor for hyperkalemia in one of these studies, the other one failed to show any correlation between rising potassium level and diabetes mellitus. These are some studies done on patients with normal kidney function. To our knowledge, the only study performed on the effect of LMW heparins, as an anticoagulant for hemodialysis, on serum potassium, was the one done by Hottelart and coworkers.[15] They carried out a cross-over study on 11 hemodialysis patients and compared UF heparin and LMW heparin after 2 weeks of trial, each regimen lasting for 1 week. They found higher predialysis potassium level in the UF heparin group with lower mean plasma aldosterone-plasma renin activity ratio; however, they were not able to conclude that LMW heparin has any effect on aldosterone synthesis or not.

Considering lack of evidence, we decided to perform a study with longer duration and higher number of patients. Our study was done at 2 hemodialysis units on 58 patients. Following 3 weeks of switching UF heparin to LMW heparin enoxaparin in 29 patients, serum potassium level was significantly lower compared to those who continued to receive their usual dose of UF heparin. While Hottelart and coworkers excluded diabetic patients, we included them in the analysis. In contrast to the diabetic patients in the UF heparin group who did not experienced any changes in serum potassium level, those in the LMW heparin group had a reduction in serum potassium level, although it was not statistically significant. The inability of enoxaparin to reduce serum potassium level could be due to the effect of diabetes mellitus on aldosterone synthesis, which results in hypoaldosteronism.[23] Unequal distribution of the diabetes mellitus in our groups is one of the weaknesses of the present study, which could have an impact on the results.

These findings reveal the role of LMW heparins in reduction of serum potassium in those who used to be on UF heparin (especially in nondiabetics), while there was no significant difference between indirect markers of nutrition and hemodialysis efficacy (urea, creatinine, and phosphate) at baseline and the end of the study. If we had serum levels of aldosterone and plasma renin activity, then the precise mechanism underlying these changes could have been determined as well as the impact of LMW heparin on aldosterone synthesis. As we were not able to compare enoxaparin with a non-heparin-containing anticoagulant, we cannot determine whether enoxaparin has any effects on

serum potassium at all or not. Another limitation of the present study was lack of data regarding serum albumin, hemodialysis adequacy indexes and urine volume, which could clarify the exact role of nutrition, hemodialysis adequacy, and residual kidney function in the obtained results.

CONCLUSIONS

Our study revealed the role of LMW heparins as a potential alternative to UF heparins in hemodialysis patients with hyperkalemia. Although the exact mechanism is not yet clear, LMW heparins could be the subject of future studies to determine their role in reducing the mortality attributed to hyperkalemia.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Jamshid Roozbeh, MD
Department of Internal Medicine, Nemazee Hospital, Zand Ave, Shiraz, Iran
Fax: +98 711 6474316
E-mail: roozbehj@hotmail.com

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