Comparative Study between Low Molecular Weight Heparin and Unfractionated Heparin on Lipids in Hemodialysis Patients

Ahmed Rabie El-Arbagy, MD[1], Mahmoud Abd El-Aziz Kora, MD[1], Hany Said El-Barbary, MD[1], Mohammed El-sayed Omara, M.B.B.Ch[2]

[1] Internal Medicine Department, Faculty of Medicine, Menoufia University, Egypt
[2] Nephrology Department, Zefta Hospital, Gharbia, Egypt
dr.garfield85@gmail.com

Abstract: Objective: To evaluate effects of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) on the level of triglycerides, cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) on hemodialysis patients. **Background:** End stage renal disease (ESRD) patients have a high risk of mortality, with cardiovascular diseases (CVD) being the commonest cause of death. Dyslipidemia is a major cause of CVD. A number of studies had evaluated the effect of both UFH and LMWH on lipid metabolism in ESRD patients. **Methods:** This study subjecting fifty patients with ESRD onmaintenance hemodialysis (HD) and last for six months. Twenty five patients using LMWH (enoxaparin) (9male and 16female) with mean age of 54.280 ± 6.668years and twenty five patients using UFH (13 male and 12 female) with mean age 56.920 ± 9.050 years. Serum cholesterol, triglycerides, HDL and LDL were determined. Demographic data and laboratory values were evaluated. **Results:** Our results show no significant difference between both groups regarding triglycerides level after the study (P=0.741) with more numerical decrease in triglycerides level in LMWH group (P=0.244). A significant increase in cholesterol level were found in UFH group after the study (P=0.009). Also the results show a significant increase in bleeding events in UFH group (P=0.020) and significant increase in coagulation problems in LMWH group (P=0.024). **Conclusions:** The results of this study indicate a more decrease in triglycerides level in patients using LMWH than UFH with significant increase in cholesterol level in UFH group. There were a significant increase in bleeding events in UFH patients and an increase in coagulation events in patients using LMWH. So we suggest using LMWH in patients with high serum cholesterol, triglyceridesand history of bleeding disorders and using UFH in patients with coagulation disorders.

[Ahmed Rabie El-Arbagy, Mahmoud Abd El-Aziz Kora, Hany Said El-Barbary, Mohammed El-sayed Omara. **Comparative Study between Low Molecular Weight Heparin and Unfractionated Heparin on Lipids in Hemodialysis Patients.** *Stem Cell* 2017;8(3):21-25]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 3. doi:10.7537/marsscj080317.03.

Keywords: Hemodialysis, Unfractionated heparin, Low molecular weight heparin.

1-Introduction

Today, chronic kidney disease (CKD) is considered a major public health problem ***(1)***. Endstage renal disease (ESRD) is a late stage of CKD that need renal replacement therapy as hemodialysis ***(2)***. End stage renal disease (ESRD) patients have a high risk of mortality, with cardiovascular diseases (CVD) being the commonest cause of death ***(3)***. Dyslipidemia plays a great rolein the high risk of CVD in hemodialysis patients but still an underestimated problem ***(4)***.

During HD, Anticoagulants are needed in order to prevent activation of the coagulation system and the subsequent platelet aggregation and formation of fibrin clot which will cause dialyzer dysfunction ***(5)***. LMWH is increasingly used in HD in addition to UFH which is the anticoagulant of choice worldwide due its low cost, safety and relative ease to use ***(6)***. Lipid metabolism is affected by UFH due to release of lipoprotein lipase enzyme (LPL) from vascular endothelium to blood stream ***(7)***. Repeated administration of UFH leads to depletion of LPL and cause slowing the lipoproteins metabolism ***(8)***. The question of whether LMWH affects plasma lipase to the same extent as UFH is still unresolved ***(9)***. The differences between heparin and LMWH are minimal in most of studies ***(10)***.

2-Patients and Methods:

This study has been conducted on a total of 50 patients which are on chronic hemodialysis program. They were divided into two main groups: twenty five patients had been treated with LMWH (enoxaparin) (9male and 16female) with mean age of 54.280 ± 6.668years and twenty five patients had been treated with UFH (13 male and 12 female) with mean age 56.920 ± 9.050years. According to sex and age, the difference between groups was insignificant (P=0.254 and P=0.246, in order). At the beginning of the study, patients' demographic and clinical characteristics and routine laboratory parameters were recorded. All patients were on 4-hour bicarbonate dialysis. Informed

consent was obtained from all study participants. The criteria of Inclusion included patients on hemodialysis program for more than 6 months and not receiving oral anticoagulants, immunosuppressive therapy or drugs affecting lipid metabolism. We exclude patients who has diagnosed with acute illnesses as gastrointestinal bleeding, any other chronic diseases as diabetes and malignancies and patients who had switched to another dialysis center.

Kits from (DIALAP COMPANY) were used to measure the serum levels of triglycerides, cholesterol, HDL and LDL. The references for these serum levels were up to 200 mg/dl for cholesterol and triglycerides levels, up to 130 mg/dl for LDL and 35.3 to 79.5 mg/dl for HDL. Kits from (BIOMED COMPANY) were used to measure prothrombin time (PT) and partial thromboplastin time (PTT). The control time for them were (13.7 and 28-40 seconds, in order).

Data management:

Statistical analysis was carried out via Statistical package for social Science (SPSS) version 17 program on windows 7. Qualitative data were represented in the form of number and percentage, while quantitative data were represented in the form of mean ± standard deviation (mean±SD). Kolmogrov-smirnov test was used to test normality of quantitative data. $\chi 2$, one-way analysis of variance (ANOVA), and Kruskal–Wallis tests were used to compare groups. Spearman's Rank correlation test was used to study correlation between parameters. Results were considered significant if p value is less than or equal 0.05.

3-Results:

Group I (enoxaparin group) consisted of 25 patients (9male and 16female) with mean age of 54.280 ± 6.668, and group II (UFH) included 25 patients (13 male and 12 female) with mean age 56.920 ± 9.050 years. Range of dialysis duration/years is 2.5-7 years for both groups, all participants undergo 3 dialysis sessions/week. There were a significant increase in BMI in group I in comparison to group II (P=0.024). Demographic and clinicaldata of participants in each group are shown in table (1) and table (2).

Table (1): Demographic data of different groups of the study

		Group I (n=25)	Group II (n=25)	P-value
Sex	**Male**	9(36.00%)	13(52.00%)	0.254 (Chi-Square)
	Female	16(64.00%)	12(48.00%)	
Age	**Range**	44-69	24-70	0.246 **(T-Test)**
	Mean ±SD	54.280 ± 6.668	56.920 ± 9.050	

Group I (On enoxaparin) Group II (On heparin) n = Number

Table (2): Clinical data in both groups

		Group I (n=25)	Group II (n=25)	P-value
Duration of Dialysis (years)	**Range**	2 - 7.5	2 - 7.5	0.818 **(T-Test)**
	Mean ±SD	4.217 ± 1.397	4.318 ± 1.667	
Duration of session (hours)	**Range**	3 - 4	3 - 4	X
	Mean ±SD	3.83 ± 0.3	3.83 ± 0.3	
Frequency of session per week	**Range**	3 - 3	3 - 3	X
	Mean ±SD	3.000 ± 0.000	3.000 ± 0.000	
BMI	**Range**	20 - 41	20 - 33	0.024* **(T-Test)**
	Mean ±SD	29.840 ± 5.720	26.680 ± 3.614	

Group I (On enoxaparin) Group II (On heparin) n = Number

Table (3) and Figure (1) showed a significant change by increase in group I in cholesterol level after the study if compared with cholesterol level before the study (P=0.009) with no significant changes in group II (P=0.188), there were a significant difference in cholesterol level between both groups after the study (P=<0.001). Also results shown more numerical decrease in triglycerides level in group I with no significant changes in group II or difference between both groups after the study as (P=0.244, P=0.932 and P=0.741, in order). The study results revealed no significant changes in HDL levels in group I (P=0.749) or in group II (P=0.294) with no significant difference between both groups (P=0.652). The results also showed no specific changes in LDL levels in both groups before and after the study as (P=0.176 and P=0.070, in order). A significant increase in LDL levels in group I after study in comparison to group II was present (P=0.002).

There was a significant increase in coagulation events (Coagulation of blood during dialysis session, creation of fibrin ring in venous dropper, occlusion of femoral and internal jugular catheter) in enoxaparin group (P=0.024) with a significant increase in bleeding events (Menorrhagia, bleeding gumsand delayed closure of AV fistula) in UFH group (P=0.020) as shown in table (4).

Table (3): Comparison between lipid profile level changes in studied groups

			Group I			Group II			P-value (T-Test)
Cholesterol	**Before study**	**Range**	142	-	310	90	-	269	<0.001*
		Mean ±SD	202.040	±	41.483	151.192	±	47.037	
	After study	**Range**	129	-	312	96	-	263	<0.001*
		Mean ±SD	209.917	±	47.620	158.320	±	45.697	
Difference		**Mean ±SD**	-6.750	±	24.374	-7.128	±	12.642	
Paired T-test		**P-value**	0.188			0.009*			
Triglycerides	**Before study**	**Range**	50	-	506	102	-	233	0.600
		Mean ±SD	176.040	±	104.157	164.268	±	39.808	
	After study	**Range**	56	-	350	107	-	251	0.741
		Mean ±SD	170.000	±	80.635	163.800	±	45.858	
Difference		**Mean ±SD**	10.375	±	42.511	0.468	±	27.157	
Paired T-test		**P-value**	0.244			0.932			
HDL	**Before study**	**Range**	19	-	44	19	-	39.8	0.445
		Mean ±SD	32.868	±	6.945	31.472	±	5.820	
	After study	**Range**	20	-	47	21	-	109	0.652
		Mean ±SD	32.833	±	7.722	34.520	±	16.568	
Difference		**Mean ±SD**	-0.271	±	4.094	-3.048	±	14.194	
Paired T-test		**P-value**	0.749			0.294			
LDL	**Before study**	**Range**	46.6	-	237	29.4	-	195.4	0.003*
		Mean ±SD	133.204	±	45.824	90.080	±	49.736	
	After study	**Range**	72	-	241	29	-	197.8	0.002*
		Mean ±SD	142.392	±	46.167	97.428	±	50.308	
Difference		**Mean ±SD**	-8.471	±	29.694	-7.348	±	19.392	
Paired T-test		**P-value**	0.176			0.070			

Group I (On enoxaparin) Group II (On heparin) HDL= High density lipoprotein LDL= Low density lipoprotein

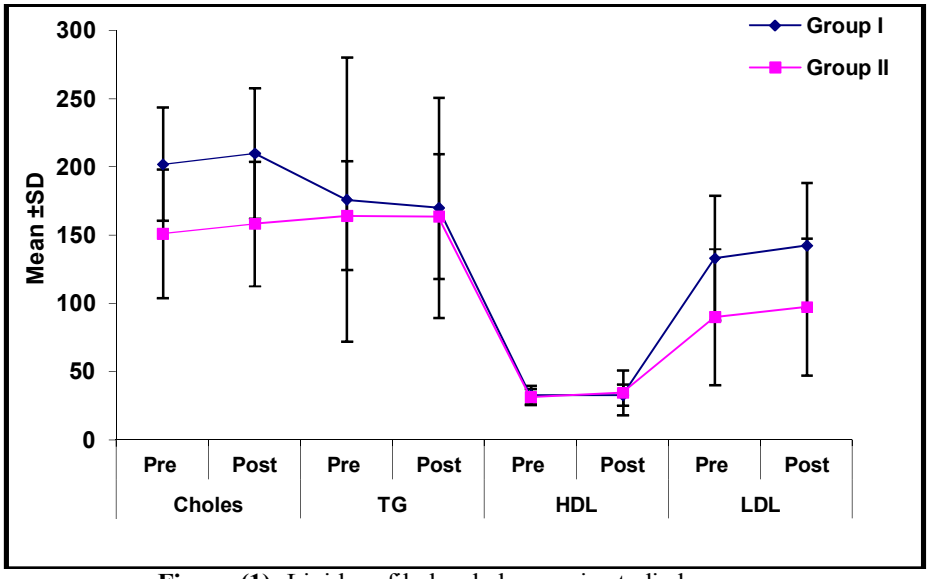

Figure (1): Lipid profile level changes in studied groups.

Table (4): Comparison between group I and group II as regard bleeding and coagulation disorders

		Group I		Group II		P-value
		N	%	N	%	Chi-Square
Bleeding disorders	**Negative**	22	91.67	16	64.00	0.020*
	Positive	2	8.33	9	36.00	
Coagulation disorders	**Negative**	16	66.67	23	92.00	0.024*
	Positive	8	33.33	2	8.00	

4-Discussion

One of the major causes of mortality and morbidity in ESRD is CVD. Dyslipidemia has been known to be traditional risk factor for CVD in the general population and it is well known that CKD patients exhibit significant alterations in lipoprotein metabolism ***(11)***. Extracorporeal blood flow is a requirement in HD. Unfractionated heparin is the anticoagulant of choice for most maintenance hemodialysis worldwide because of its low cost and safety. LMWH have increased in use recentlyas it showed a lower incidence of heparin side effects such as thrombocytopenia and osteoporosis ***(6)***.

In our study, There were a significant increase in serum cholesterol level after the study in UFH group (P= 0.009) and a numerical but not significant increase in cholesterol level in LMWH group (P=0.188). In agreement with the study of Nassiri and colleagues about effect of heparin and LMWH on oxidative stress in hemodialysis patients in which there were in cholesterol levels in both groups (P=<0.001 and P=<0.001, in order). In comparison between both groups regarding cholesterol level changes the results showed increase cholesterol level after study in both groups with more increase in group I (P-value = <0.001*). In disagreement with the results of resic and colleagues study comparing effect of heparin and LMWH on lipids in hemodialysis patients which showed no significant changes in cholesterol level between the two groups. This differences possibly due to increase BMI and poor diet control in this group of study. The results in group I regarding changes in triglycerides after study showed numerical decrease in triglycerides level (P=0.244) in agreement with Resic and colleagues results. Also the results in group II regarding mean triglycerides level were (164.268± 39.808, 163.800 ± 45.858, respectively) with (P = 0.932). In agreement with the study of Tabiban and colleagues comparing effect of enoxaparin and heparin for hemodialysis Anti coagulations where mean triglycerides levels were respectively (139.28 ± 48.13, 136.53 ± 56.5). In comparison between both groups regarding triglycerides levels the results showed no significant changes in levels (P = 0.741). In agreement with the results of Mahmood and colleagues study about lipoprotein lipase response to UFH and LMWH in hemodialysis.

HDL changes comparison showed no significant changes in HDL levels in group 1 after the study (P =0.749). Group II showed also no significant changes in HDL levels (P=0.294) in agreement with the results of Tabiban and colleagues and in disagreement with the results of **Nassiri** and colleagues which showed significant increase in HDL levels in both groups (P= < 0.001* and P= < 0.001*, in order). This difference possibly due to differences in nutritional habits. Also there were no significant difference between the two groups after the study (P=0.652). In agreement with results of Shantha and colleagues study about efficacy and safety of LMWH in comparison with heparin in chronic hemodialysis. Our study showedsignificant increase in LDL levels in group 1 if compared by levels of group II (P=0.002). In disagreement with results of Tabiban and colleague and Gritters and colleague resultsthat showed no significant difference between the two groups. This difference due to difference in nutritional habits and also high LDL level in group I before the occurrence of the study.

Furthermore, we studied the incidence of occurrence of bleeding, coagulation disorders as regard the type of heparin in different study groups and we found significant increase in coagulation disorders as (Coagulation of blood during dialysis session, creation of fibrin ring in venous dropper, occlusion of femoral and internal jugular catheter) in group I in agreement with the results of Herrero-Calvo and colleagues results that showed increase in coagulation events in LMWH group (P=0.003) and in disagreement with the results of Abdallah and colleagues that showed no significance difference in thrombotic changes between both groups. This disagreement possibly due to difference of dose enoxaparin used in the two studies.

There were a significant increase in incidence of bleeding problems as (Menorrhagia, bleeding gums and delayed closure of AV fistula) in group II (P=0.020) in agreement with the results of Li and colleagues which also showed increase in bleeding events in UFH group (P = 0.00).

Conclusions and Recommendations:

Our study showed anincrease in cholesterol levels and incidence of bleeding events in UFH group with numerical decline in triglycerides level and significant increase in coagulation events in LMWH group. So we suggest usingof LMWH drugs in patients with high serum cholesterol, triglycerides and history of bleeding disorders and using of UFH in patients with history of coagulation disorders. However, the anti-coagulants effect on lipid metabolism in hemodialysis patients is still unclear. Further studies with higher number of patients are required.

References

1. Mikolasevic I, Zutelija M, Mavrinac V, et al. Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renovasc Dis2017; 10: 35-45.
2. Meyer TW, Hostetter. Uremia. N engl j med 2007;357:1316-1325.
3. De jager DJ, Grootendorst DC, Jager KJ, et al. Cardiovascular and non-cardiovascular mortality among patients starting dialysis. *JAMA 2009 302:1782-1789.*
4. Kronenberg F, Lingenhel A, Neyer U, et al. Prevalence of dyslipidemic risk factors in hemodialysis and CAPD patients. Kidney Int Suppl. 2003;(84):S113-116.
5. Stefoni S, Cianciolo G, Donati G, et al. Standard heparin versus low molecular weight heparin. A medium-term comparison in hemodialysis. Nephron 2003; 92(3): 589-600.
6. Tabiban S, Rahbar K, Ghadrdoost B, et al. Comparison of enoxaparine sodium and standard heparin for hemodialysis anti coagulation. Nephrourol Mon 2017; e 43443.
7. Tsai MH, Fang YU and Leu JG. Tinzaparin Provides Lower Lipid Profiles in Maintenance Hemodialysis Patients: A Cross-Sectional Observational Study. SWJ 2014; 486781.
8. Näsström B, Stegmayr B, Gupta J, et al. A single bolus of a low molecular weight heparin to patients on haemodialysis depletes lipoprotein lipase stores and retards triglyceride clearing. Nephrol Dial Transplant 2005;20(6): 1172-1179.
9. Mahmood D, Grubbstrom M, Di Lundberg L, et al. Lipoprotein lipase responds similarly to tinzaparin as to conventional heparin during hemodialysis. BMC Nephrology 2010; 11: 33.
10. Resić H, Kukavica N, Šahović V, et al.Different effects of low weight molecular heparin and unfractioned heparin on lipid profile and coagulation at haemodialysis patients. Bosn. J. Basic. Med. Sci2010; 10: s56-s62.
11. Tsimihodimos V, Mitrogianni Z and Elisaf M. Dyslipidemia associated with chronic kidney disease. The open cardiovascular medicine J 2011; 5: 41-48.
12. Nassiri A, Hakemi M, Soulati M, et al. Effect of heparin and dalteparin on oxidative stress during hemodialysis with end stage renal disease. IJKD 2009; 3: 162-167.
13. Shantha GP, Kumar AA, Sethi M, et al. Efficacy and safety of low molecular weight heparin compared to unfractionated heparin for chronic outpatient hemodialysis in end stage renal disease: systematic review and meta-analysis. Peer J 2015, DOI 10.7717/peerj.835.
14. Gritters M, Grooteman MPC, Schoorl M et al. Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. Nephrol Dial Transplant 2006; 21:153–159.
15. Herrero- Calvo JA, Gonzalez-Para E, Garcia-Perez R, et al. Spanish study of anticoagulation in hemodialysis. Nefrologia 2012; 32(2): 143-152.
16. Abdallah E, El-Shishtawy S and Mosbah O. Safety and efficacy of low molecular weight heparin (enoxaparin sodium) in comparison with standard unfractionated heparin for hemodialysis anticoagulation. African Journal of Nephrology 2015; 18(1): 6-11.
17. Li RF, Cui XQ and Xu LP. Anticoagulant effect of low molecular weight heparin on central venous catheters in haemodialysis patients. Trop J Pharm Res 2016; 15(12): 2733-2738.

5/23/2017