DIFFERENT EFFECTS OF LOW WEIGHT MOLECULAR HEPARIN AND UNFRACTIONED HEPARIN ON LIPID PROFILE AND COAGULATION AT HAEMODIALYSIS PATIENTS

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Abstract

Each haemodialysis treatment requires the application of anticoagulation medicines, which will prevent coagulation in extracorporal blood circulation. In this study we try to determine the quality of admitted anticoagulant and his effect on lipid profile on hemodialysis patients after twelth months. We were applying standard heparin and low weight molecular heparin (LWMH). During our study we was analyzed effect of anticoagulant therapy on lipid profile of hemodialysis patients. In that parameters was included triglycerides, cholesterol, lipoprotein fractions, complete blood count, Hgb, HCT; All of these parameters was analyzed in correlation with duration of hemodialysis treatment, sex and age of the patients. Our research was carried out as a prospective study, for the period of 12 months. In the study were included 60 patients (34M/26F), who were on chronic hemodialysis program. All patients were divided into two groups. The first group of patients was included 27 patients (15M/12F) who were treated with standard heparin. The second group was included 33 patients (19M/14F) treated with LWMH (enoxaparin). The average length of hemodialysis was 4,15 ± 0,52 years. Each patient had a protocol in which is marked parameters such as flushing diallysator, creating fibrin-ring in vein and arterial dropper and the time it takes to stop the bleeding. In the results the average age amounted to 58,54 ± 2,24 years. The average value of cholesterol in the blood was 5,38 ± 2,26. Values of HDL-cholesterol in patients treated with LWMH were significantly lower (P≤0,05) in the treated group compared to standard heparin. There were no significant statistical differences between both groups in relation to the level of LDL cholesterol in the blood. (p ns). LWMH had a better effect on the irrigation system and dialysator on both sex equally, compared with standard heparin. LWMH is in the female dialysis population has led to improvements in lipid profile. After the first six months of study in male patients treated with standard heparin in relation to the female part of the observed patients was significantly better anticoagulation effect in the first half of the study (1,85 ± 0,05 compared to 2,09 ± 0,10) (P≤0,001). Average rating blood clots were statistically significant for standard heparin (p≤0,001) with 1,86 at the beginning the value is fell to 1,41, while for LWMH with 1,85 at the beginning of the study amounted to 1,52 grade average. (P≤0, 05). The results of our study show that LWMH had a better rinsing effect of dialysis systems and dialysator in both sex equally, compared to standard unfractioned heparin. When

the male part of the respondents in the first six months of standard heparin had a better evaluation of blood clots than women in the same group, and also better than the group on enoxaparin for both gender. LWMH in female dialysis population has led to improved lipid profiles. Patients treated with standard heparin had a statistically significant reduction in the rate of blood clots than patients who received enoxaparin (LWMH).

Such differences were minimal, which can be interpreted by the fact that LWMH still derivative of the standard heparin

KEY WORDS: haemodialysis, lipid profiles, standard heparin, LWMH (enoxaparin);

Introduction

Hemodialysis and continuous renal function replacement techniques require removal of blood outside of the body in extra corporal circulation for process of blood purifying and filtration. To prevent blood coagulation during hemodialysis in treatment we must include anticoagulation therapy, (usually give heparin). After hemodialysis treatment we monitoring parameters INR and APTT which enables proper dosage of given anticoagulant in therapy. Determination of APTT and INR has the advantage compared to determine the total time for blood clotting and simple methods for very rapid interpretation of results. Generally, many dialysis centers do not routinely determine the parameters of anticoagulation until you reach certain complications such as clots in dialysator and dialysis system, or prolonged bleeding time in patients after HD. In order to reduce the risk of bleeding after HD treatment, in dialysis centers give the lowest dose of heparin to patients which is sufficient to make complete hemodialysis treatment without fear that there will be coagulation or cloth formations of blood in dialysator, artherial or vein dropper, or in the system. Anticoagulation in hemodialysis treatment is performed using low weight molecular heparin (LMWH) that was proposed in order to reduce complications of bleeding and reduce the appearance of thrombocytopenia, such as complications that is present with the treatment of standard heparin. Also, LWMH it was had better effects on lipid profile on hemodialysis patients. However, numerous randomized studies have shown that differences between LWMH and standard heparin is almost minimal.

Aim

The aim of this work was to evaluate effects of standard heparin and Low Weight Molecular Heparin (LWMH) on the level of triglycerides, cholesterol, lipoproteins on hemodialysis patients and their anticoagulant effect, and relation this parameters on sex and age of patients, as well as examining the correlation between the length of HD and age of the patients.

Materials and Methods

Patients

In this study were included 60 patients (34 men and 26 women), which are on chronic hemodialysis program for the period longest than six months, with a different etiology of renal disease. All subjects were divided into two groups. **The first group** of respondents, 27 of them was treated with standard heparin. In this group the sexual distribution was 15 men and 12 women. The average age for women was 50.07, while the men amounted to 61 years; the average length of hemodialysis was 3,44 ± 0,49 years. Application heparin was done continuously during the HD (the pump is programmed to stop the car 20 minutes before the end of HD treatment) **The second group** of 33 subjects were constituted treated with low-heparin (LWMH). In this group there were 19 men (56,6%) and 14 women (42,4%). The average age was 58,54 ± 2,24 years. The average age for men was 56,05, while for women amounted to 61,93 years. The average length of hemodialysis was 4,15 ± 0,52 years. Low-heparin was given at the beginning hemodialysis treatment in a dose subcutaneous particularly adapted to each patient.

Inclusion criteria:
- That are longer than six months to hemodialysis program
- To have elevated levels of triglycerides and cholesterol
- Not receiving oral anticoagulation therapy
- Not receiving drugs that affect the metabolism of lipids (Statins, renagel)
- That are not on immunosuppressive therapy

Exclusion criteria
- Switch of patients to another dialysis center or transplant kidney
- Occurrence of an acute illness (gastrointestinal bleeding, gynecological hemorrhage) when the patient is dialyses without of anticoagulation

- Patients with diabetes, malignancy, severe liver disease
- Patients who had an inflammatory or infectious disease the previous months
- Lethal outcome

The laboratory findings were analyzed:
- Triglycerides, cholesterol, lipoprotein fractions
- Complete blood count, hemoglobin, hematocrit, iron and ferritin
- All parameters should be determined at the beginning of the study and then every three months.
- INR, APTT, coagulation time at the beginning of the study and then quarterly

Methods

The survey lasted twelve months; data from the completion of laboratory tests were taken every three months during the study, were then grouped into half-yearly results and for the period January-June and July to December. Patients were on HD three times a week by four hours (bicarbonate dialysis), low-flux dialysate, dialysis monitors of firm Fresenius Medical Care, 4008S with UF. The research was conducted at the Clinic for hemodialysis, and Institute of Clinical Chemistry and Biochemistry. It was a retrospective prospective controlled study. Standard heparin was applied in doses of 40 to 50 UI/kg and on continuously (on average from 3000 to 5000 UI for four hours duration of hemodialysis). Low-heparin it was enoxaparin (Clexan) in a dose of 40 mg, which was gave in a single dose in the arterial part of the dialysis system. Also considered were taken and data personal history, family history and co morbid conditions. Blood coagulation a test was taken from arterial dialysis lines, front seats heparin infusion, so the test reflects the state of the system of patient's anticoagulation.

Each patient had a protocol in which after every HD evaluated the effect of admitted anticoagulation:
1. Flushing of dialysator
2. Creation fibrin ring in vein and arterial dropper
3. Time to stop bleeding

Usually, after a complete HD found several coagulated capillaries (up to 5), and a small donut clot in the vein dropper. Capillaries are in dialysator consisting of a transparent plastic cylinder in which there are thousands of capillary wipes made of dialysis membrane. Blood flows through the wipes, and with their external surfaces dialysis fluid flows, and thus had a clear view

emerging number coagulating capillaries. Counting of coagulated capillaries after each hemodialysis in the following manner valuates adequate anticoagulation:
- 0 Excellent grade rinsed 5 capillary
- 1 Rating of 5 to 10 capillaries
- Grade 2 since 10 to 15 capillaries
- 3 Vote of 15 to 20 capillaries
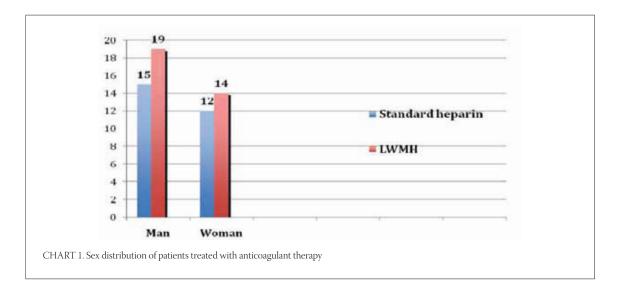- 4 Vote of 20 to 25 capillaries
- Rating - 5> 25 capillaries

Rinse dialysator shows how many of capillary is coagulating (so that the counting of the number of coagulating capillaries performed the evaluation).

Statistical analysis

Results were statistically analyzed to determine average value (x), standard deviation (SD) and standard error mean (SEM) for each monitored parameter within the group. Differences between the values determined by Student t-test and chi-square test ($\chi2$). Values less than 0,05 taken as significant. Correlation between compared parameters determined by Spearman-in, Wilcox's method.

RESULTS

The research was conducted on 60 subjects for a period of twelve months. All subjects were on chronic hemodialysis program in more than six months, with a different cause of chronic kidney misfire. All subjects were divided into two groups. The first group of consisted of 27 subjects treated with standard heparin, and another group of consisted of 33 subjects treated with LMWH. Laboratory analysis of the findings of blood was performed every three months during one year how much time research. Data obtained were analyzed as data and information at the beginning of the end of the study. From chart 1 we can note that the women are on average older age than men and in both examined groups. Total number of age for men in the standard heparin treated group was 50,07 years and women 61 years. Average age for men in the group treated with low-heparin was 56,05, while for women the same age group the average amounted to 61,93 years. The causes that led to chronic renal failure in our patients were varied. Nephroangisclerosis is the leading cause and participate with 49,15% in the etiology of chronic renal failure, followed by urinary obstruction for the following times 32,20% while the hereditary renal diseases participated with 30,51%.

CHART 1. Sex distribution of patients treated with anticoagulant therapy

	Sex				Total	
	Male		Female			
	N	%	N	%	N	%
Heparin	15	55,6	12	44,4	27	45
Enoxaparin	19	57,6	14	42,4	33	55
Total	34	56,7	26	43,3	60	100

TABLE 1. Sex distribution of patients which was treated with standard and LWMH

Grade of blood clothing	Man		Female	
	Rate	%	Rate	%
0	5	1,5	5	2,2
1	134	39,3	81	36,7
2	135	39,6	88	39,8
3	47	13,7	36	16,3
4	15	4,4	7	3,2
5	5	1,5	4	1,8
Total	341	100	221	100
x±SEM	1,85±0,05		2,09±0,10	
p<	NS			

TABLE 2. Results the evaluation of clotting for the respondents of both gender treated standard heparin at the beginning of the study

Rate heparin for blood clots in both the years for men and women was not significant.

Grade of blood clothing	Man		Female	
	Rate	%	Rate	%
0	7	2,7	3	1,7
1	151	59,2	93	52,8
2	93	36,5	75	42,6
3	4	1,6	4	2,2
4	-	-	1	0,6
5	-	-	-	-
Total	255	100	176	100
x±SEM	1,37±0,035		1,47±0,046	
p<	NS			

TABLE 3. Results evaluation of clotting for the respondents of both gender treated with standard heparin at the end of the study

From the Table 3. we see that for the second period of monitoring (from July to December 2007.) subjects who received heparin in the second half had a statistically significant decrease evaluate of blood clots compared to patients who received enoxaparin, which means better flushing of hemodialysis systems, and arterial and vein dropper.

The rate of blood clothing	I total findings	
	Rate	%
0	10	1,78
1	215	38,26
2	223	39,68
3	83	14,77
4	22	3,91
5	9	1,60
Total	562	100

TABLE 4. The overall results of evaluation of blood clots for the respondents either sex treated with standard heparin

The result of testing the found in the average evaluation of blood clots shown in the table ????? 30th for enoxaparin were analyzed according to gender in both time periods. Differences in blood coagulation for low-heparin for the first six months, according to gen-

Grade of blood clothing	Man		Female	
	Rate	%	Rate	%
0	16	3,8	14	4,3
1	134	31,9	98	30,1
2	204	48,6	137	42,0
3	53	12,6	61	18,7
4	9	2,1	11	3,4
5	4	1,0	5	1,5
Total	420	100	326	100
x±SEM	1,80±0,04		1,91±0,05	
p<	NS			

TABLE 5. Results of rate blood clots at the beginning of the study, patients treated with LWMH

der was statistically mainly negative, while the following year, the difference is more pronounced. (Table 5).

Grade of blood clothing	Man		Female	
	Rate	%	Rate	%
0	3	0,9	3	1,2
1	185	57,1	116	44,6
2	124	38,3	122	46,9
3	10	3,1	19	7,3
4	2	0,6	-	-
5	-	-	-	-
Total	324	100	260	100
x±SEM	1,45±0,034		1,60±0,039	
p<	NS			

TABLE 6. Results of rate blood clots at the end of the study, patients treated with LWMH

Discussion

Atherosclerotic changes on hemodialysis patients are multifactor conditioned. That's the causes of increased of morbidity and mortality in dialysis population. One of risk factor is hyperlipidemia, which accelerates atherosclerosis and which also leading to increase prevalence of cardiovascular disease and the increases of mortality in hemodialysis population. Dyslipidemia, is primarily mean increased values of triglycerides in the blood and decrease levels of "protective" HDL-cholesterol and increase levels of low-density lipoprotein (LDL), which operate jointly with disorders in blood coagulation and metabolic disorders. In our dialysis population increased levels of triglyceride in the blood iwas 80% of patients at the beginning of the study. Characteristics of uremic dyslipidemia were hypertriglyceridemia, the increase of the remaining lipoprotein (remaining Chylomicron and IDL-a), reduced HDL-cholesterol, and increase in SD-LDL, Lp (a) and ApoA-IV.[1] Control of these parameters was performed in our clinic every three months. At the beginning of the study was observed elevated levels of LDL cholesterol by 14% of respondents. Total LDL cholesterol levels was often normal in chronic renal disease and patients which was on chronic hemodialysis treatment, but is usually found elevated levels sdLDL, IDL, LDL, which are probably more atherogenic. Equally, clinical studies do not distinguish between LDL-A, Lp (a) and their LWMH isoform, which are independent risk factors for atherosclerotic disease and are often elevated in chronic kidney disease, but analysis of these isoform was technically managed for our study. IDL cholesterol is often elevated in uremia. Unfortunately, current clinical trials do not distinguish between LDL cholesterol and IDL cholesterol. There-

fore, some clinical trials may not assess the emergence atherosclerosis exact cholesterol loaded in uremia.[6] Our study also has not been specifically processed IDL cholesterol. Influence of LWMH heparin and standard heparin on the concentration of total cholesterol showed no significant statistical difference at the end of our research. While studies have not noticed favorable effects LWMH and standard heparin on the concentration of total cholesterol in plasma for both groups of respondents. LWMH was no showed expected lipolitycal effect, coincides with the results of research he spent Kronenberg et al. [3] The fact that the low-heparin showed minor differences according to gender through the same treatment period than is the case with standard heparin. Even his influence and the effect are more favorable with the male part of the tested population, but women throughout the period of follow-up study. However, enoxaparin showed mainly negative decline in the level of HDL cholesterol at the end of the study, which was not expected, nor was positive for patients. Standard heparin showed no significant deviations from the beginning until the end of the study spent. The difference to the sexual distribution of standard heparin was significant and gave better results in men than in women's part of respondents. Influence of standard heparin on LDL cholesterol is such that the mean value of 3,008 down to 2,745 which is positive, also came up with the fall of HDL cholesterol values of 1,027 to 0,886 in the second period which is not favorable effect, but it was expected, also comes treiglicerida to fall with the value 2,008 to the value of 1,890 which is also a positive effect but he was not expected. In cross-study conducted by Deuber and Schulz (4) was showed data were taken from five patients who received standard heparin, LMWH after a period of 12 months, then again returned to standard heparin, While receiving LMWH, there was a significant reduction of the concentration of triglycerides and cholesterol in the blood, In other studies, cholesterol values were decreased between 8-20% in the period of treatment with LMWH for a period of monitoring from 6 to 48 months (2, 7), however, while there was no change in the value of cholesterol in the course of giving LMWH, which is followed in the study by Schrader spent and out, As also coincides with our study (5), Effect of LWMH is slightly different and its influence on HDL cholesterol in the first period of investigation amounted to 1,107, while for the second period of monitoring of its high value of 0,942 was statistically significant and unexpected differences. There are not mainly negative values decrease LDL cholesterol values from 2,924 to 2,816, which is expected and

good, but should be much higher. LWMH effect on triglyceride levels that are in the first six months of the study had a value of 2,036 to the second period, at the end of the study had a value of 1,868, which is expected and positive for our respondents. Standard heparin in the first six months of research showed slightly better effect on lowering levels of triglycerides in the blood, but the twelve months to the value of the individual subjects and showed a slight increase (at 4 patients). (7, 8) Compared with the study conducted by Lieu and authors, (6) showed how LMWH has less affinity for LPL, which has not resulted in reduced potency to the release of LPL-and, by endothelial carried in peripheral tissues, but primarily in substantially reduced effect in terms of hepatical removal of this enzyme. From a theoretical standpoint there is a possibility to switch from standard heparin in LWMH will not reduce triglyceride levels, as shown by Schmitt and Schneider's. (9). Target values for plasma lipids in patients with chronic renal disease and dialysis patients are unknown. Clinical studies the most commonly used for measuring total triglycerides, LDL and HDL cholesterol may not be fully accepted clinically relevant lipid abnormalities in uremia, such as the increase in Lp (a), IDL cholesterol, modifying LDL cholesterol and changes in HDL cholesterol sub fraction. Results of testing the found in the average evaluation of blood clots for the heparin tested periods at the beginning of the study was statistically significant, but at the end of the study was not statistically significant differences. At the beginning of the study standard heparin had a significant better effect on anticoagulation effects of blood in men than in women, while after one year follow-up of patients was not statistically significant dif-

ferences. LWMH at the beginning of the study had a far better evaluate the leaching system, and a small degree of clotting in the system, medicine dropper and dialysator of heparin. However, during the study, as well as its very end, the difference was no longer statistically significant, so that the end results were almost equal (10,11). Given the difference between the genders and the type of received anticoagulant differences were statistically very significant, so that groups of women treated with heparin had low-improving results dialysis rinsing system, dyalisator and arterial and vein dropper at the end of the study.(12) The men treated with LWMH, there was a deterioration of results leaching of dialysis, dialysat and system dropper. Rate of low-blood clotting heparin for the first time tracking the men had an average mark 1,80, while women had an average mark 1,91 (lower is better). After a year of follow-up, men who were treated with enoxaparin had an average mark clot, which amounted to 1,45, while the average grade for women amounted to 1,60 (lower is better). Thus the overall assessment of statistical significantly by gender which was significant for the first six months of study, with the level of reliability p≤0,01, while the second period tracking results also mainly negative, with a confidence level of p 0,01. The difference between both periods for men was 7,86, and 5,636 for women and a total of 9,216, all statistically significant with a confidence level of p 0,001. At the beginning of the study, all patients who started treatment hemodialysis with LMWH had better results in terms of better rinsing dialysat and systems, and better effects on the increase in HDL cholesterol and triglyceride values fall in the blood. But at the end of the study results show no significant difference between LWMH and standard heparin (14).

Conclusions

The results of our research showed that the LWMH had a better effect of leaching of the system and dialysator in both sex equally, in comparesment with the standard heparin. LWMH in women dialysis population led to the improvement of lipid profiles. Patients treated with standard heparin had a statistically significant reduction assessment of blood clots than patients who received enoxaparin (LWMH). LWMH is a good choice for anticoagulation. Found that the long-term treatment with LMWH causes gradual, not abrupt increase in the concentration of serum triglyceride and cholesterol in hemodialysis patients, in contrast to the marked hyperlipidemia as evidenced by long-term use of standard heparin present in most dialysis patients. Many factors have affect on the lipid profile of which is significant to note food that the patients according to its structure is very varied during the twelve months as the time of this research. These minimal differences LWMH and standard heparin can be attributed to the fact that it is still LWMH derivative of standard heparin. Nephrologists', and general practitioners must recognize dyslipedimia in the early stages of HBI, which has developed guidelines to the general population. It is significant to note that our study short time to effectuate the complete and detailed analysis of lipid profiles in patients on chronic hemodialysis treatment. Improvement of lipid profile in dialysis patients will certainly contribute to reducing the risk of cardiovascular complications in hemodialysis patients.

List of Abbreviations

LWMH	-	Low weight molecular heparin
Standard heparin	-	Unfractioned heparin
UF	-	Ultra Filtration
HD	-	Hemodialysis
ESRD	-	End Stage Renal Disease
SPSS	-	Analytical and statistical Software. Specializing in data mining, customer relationship management, business intelligence and data analysis.
INR	-	International Normalized Ratio - Since the Prothrombin time (PT) evaluates the ability of blood to clot properly, it can be used to help diagnose bleeding. When used in this instance, it is often used in conjunction with the PTT to evaluate the function of all coagulation factors. Occasionally, the test may be used to screen patients for any previously undetected bleeding problems.
APTT	-	Activated Partial Thromboplastin Time - As part of an investigation of a bleeding or thrombotic episode; to monitor standard heparin anticoagulant therapy.

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