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D-DIMER IN HEMODIALYSIS PATIENTS RECEIVING CONTINUOUS AND INTERMITTENT HEPARIN

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ABSTRACT

Hemodialysis is the most widely used kidney replacement therapy in Indonesia and in the world, but the procedure may trigger development in thrombogenesis. Due to this reason, anticoagulant heparin was given during hemodialysis to prevent the development of thrombus. However, hemostasis monitoring is essential to predict the possibility of heparin-induced bleeding. The use of heparin in general needs an instrument to regulate continuous heparin administration, yet, not all hospitals have devices and for this reason, some centers use intermittent heparin injection. The study aimed was to investigate whether intermittent heparin was as effective as continuous heparin to prevent thrombus formation as well as to prevent bleeding and predict the survival outcome. Patients were divided into two groups, intermittent heparin and constant heparin in a total of 50 patients. Platelet count, PT, APTT, TT, fibrinogen, and D-dimer were investigated. The results demonstrated that platelet count, PT, APTT, TT, fibrinogen, and D-dimer were not significantly different between the groups receiving intermittent and continuous heparin ($p > 0.05$). When the test was compared between intermittent and continuous heparin in pre and post-hemodialysis, it was clear that there were significant increases in APTT and fibrinogen both in the periodic and continuous heparin, but D-dimer was increased in continuous heparin only during post-hemodialysis. There was no difference in the 1-year survival outcome between intermittent and continuous heparin. In conclusion, intermittent heparin produces less D-dimer increase compared to continuous heparin, but it was as effective as continuous heparin. Intermittent heparin may be used as the choice when continuous syringe driver instrument was not available.

Key words: Hemostasis, hemodialysis, heparin, chronic kidney disease

INTRODUCTION

Chronic Kidney Disease (CKD) is a condition in which kidney function is greatly reduced.[1] Hemodialysis is a treatment of choice when glomerular filtration rate is reduced to the rate of <15mL/min/1.73m^2. The condition is called as CKD stage 5 (End-Stage Renal Disease/ESRD).[2] The new HD machine constantly evolves to the new generation of filter membrane and its tubing which made the surface become more physiological compared to the old generation.[3] Therefore, the possibility of microthrombus formation which is formed in the membrane as well as in the tubes become less and happened less.[4] However, despite this fact, there is still concern about possible thrombogenesis, and anticoagulant heparin is therefore given during the HD process.[5] The use of heparin especially continuous heparin injection is still used in general HD centers around the world.[6] Although, thrombus formation is less likely to happen, an observation about possible microthrombus formation is always carried out. Heparin as an anticoagulant may produce another adverse reaction which is bleeding.[7,8]

In some HD centers, the facility of syringe driver for the use of continuous heparin is not available, and some centers use intermittent injections of heparin as an alternative to continuous heparin. The efficacy of intermittent heparin is still unclear, whether it is as effective as continuous heparin as well as the possibility of producing a worse outcome to the patients. In addition to the efficacy, it is also important to know the dose used for intermittent and continuous heparin. The dose should be standardized based on standard HD criteria to minimize possible bias.

This study was aimed to find out whether the

intermittent heparin is as effective as continuous heparin, especially in the center where there is no continuous syringe driver facility to replace the used of continuous heparin.

METHODS

This study received approval from the local ethical committee, in this case from North Sumatera University School of Medicine/Adam Malik Hospital ethical committee, under registration number (168/TGL/KEPK FK USU-RSUP HAM/2017) and has received informed consent from the patients or their guardians. They have been explained about the protocol of the study and possible unpleasant effect that may occur during the study.

Fifty patients were recruited, and 25 who received continuous heparin, and the other 25 received intermittent heparin, and then all the patients were followed until one year to see the 1-year survival outcome. The dose of continuous heparin was 2,000 Iu as a bolus injection followed by continuous heparin injection at the rate of 1,000 Iu/hour for the whole process of HD and stopped 1 hour before the end of HD process. The dose for intermittent heparin was 2,000 Iu as a bolus injection followed by 1,000 Iu injection every hour. All patients were patients who received regular HD twice a week and therefore also received erythropoietin injection. All patients who received erythropoietin should have a ferritin level as >100mg/dL, and or transferrin saturation index (TSI) >20%. They were treated the same way for both legs; however, any other routine treatment such as anti-diabetic, anti-hypertensive, and others were given accordingly.

The inclusion criteria: patients who were 18-65 years old, had received recombinant human erytrhopoeitin (rhuEPO) of more than 3-months duration, regular HD allowed only a twice a week HD procedure. The exclusion criteria: patients consuming oral anticoagulants and used central venous catheter rather than AV fistula shunt (Cimino shunt) for dialysis.

The HD used an HD machine of Fresenius 4008B from Germany or NIPRO Sundial 55 Plus from Japan. The setting of the HD procedure was standardized using quick blood (QB) 250-300mL/min. Insertion of the line for HD for all patients was through an AV fistula shunt (Cimino shunt).

Blood sampling was carried out 5-10 minutes before the start of HD and 30 minutes after the stopping of HD. Six mL of blood was taken from a median vein, and 3 mL was put into an EDTA vacutainer, another 3 mL into a citrate vacutainer. The EDTA blood was for the investigation of full blood count while the citrated blood was used for hemostasis profile. The full blood count was performed using a Sysmex XN 1000 machine from Kobe Japan. The hemostasis profile such as Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT) was carried out using clotting-based assay from Coatron A6. Fibrinogen was tested using the Clauss method, and D-dimer assay was done based on turbidimetry of light absorbance principle by Coatron instrument from Germany.

The Statistical Package for Social Sciences (SPSS 22 IBM Corp) was used to perform statistical analysis. The basic characteristics of research subjects were presented in tabulation form and described. To assess the difference in hemostasis values of CKD group of patients pre and post HD, pairwise T-test was used if the data were normally distributed and Wilcoxon test if the data was not normally distributed. A p-value of <0.05 was considered statistically significant.

RESULT AND DISCUSSION

Fifty patients (male n= 30, female n=20) who fulfilled the inclusion criteria and who gave written informed consent were recruited. Their mean age was 49.98 ± 13.02 years and ranging between 18 and 65 years. The characteristics of the study are shown in Table 1.

Table 1. Characteristics of patients on hemodialysis

Variables	(n = 50)
Sex	
Male	30 (60%)
Female	20 (40%)
Age (years)	49.98 ± 13.02
Underlying disease:	
Hypertensive nephropathy	28 (56%)
Diabetic nephropathy	11 (22%)
Obstructive infective kidney disease	4 (8%)
Chronic glomerulonephritis	3 (6%)
Chronic pyelonephritis	2 (4%)
Polycystic kidney disease	1 (2%)
Gout-associated CKD	1 (2%)

When the platelet count, PT, APTT, TT, fibrinogen, and D-dimer were analyzed between pre HD against post-HD for both intermittent and continuous heparin it was shown that there were no significant differences between all parameters tested for

intermittent and continuous heparin for each HD cycle (pre and post) as can be seen in Table 2.

Investigation for individual intermittent heparin treatment when analyzed between pre and post-HD resulted that APTT and fibrinogen showed significant differences, whereas the APTT and fibrinogen became higher in post-HD ($p<0.0001$) and ($p<0.05$) respectively. Nevertheless, D-dimer in this group remained unchanged ($p>0.05$) as can be seen in Table 3.

A similar analysis performed in the continuous heparin group also showed increases in the APTT and fibrinogen ($p<0.0001$), but at this time D-dimer increased significantly ($p<0.005$) (see Table 4).

Table 5 showed that there was no statistical difference between patients who were still alive, and a patient who died, treated by intermittent and continuous heparin.

Table 2. Hemostasis tests in a patient receiving intermittent and continuous heparin during the pre and post hemodialysis

Tests	Pre HD			Post-HD		
	Intermittent	Continuous		Intermittent	Continuous	
	$x \pm SD$	$x \pm SD$	$p.$	$x \pm SD$	$x \pm SD$	$p.$
Platelets (10^9/L)	224 ± 92	196 ± 57	0.200	233 ± 90	204 ± 55	0.174
PT (sec)	11.78 ± 1.3	11.85 ± 1.04	0.832	11.86 ± 12.11	1.37 ± 1.06	0.474
INR	0.82 ± 0.09	0.83 ± 0.08	0.755	0.82 ± 0.10	0.85 ± 0.08	0.376
APTT (sec)	30.13 ± 4.89	30.98 ± 3.22	0.377	99.62 ± 127.91	155.69 ± 165.76	0.377
TT (sec)	19.19 ± 2.82	18.74 ± 2.51	0.263	75.83 ± 137.89	140.7 ± 189.89	0.263
Fibrinogen(mg/dL)	455.2 ± 130	439 ± 100.5	0.623	499.9 ± 140	496.7 ± 119.6	0.930
D-dimer (ng/dL)	485.8 ± 624.2	257.2 ± 180.4	0.229	516.4 ± 605.9	533.1 ± 656.0	0.229

Table 3. The difference of hemostasis value pre and post-hemodialysis with intermittent heparin

Variables	Pre HD (n = 25)	Post-HD (n = 25)	P
Platelets	22,0320 ± 92885.11	22,9040 ± 91411.83	0.316
PT	11.8 ± 1.28	11.83 ± 1.35	0.575
INR	0.82 ± 0.09	0.83 ± 0.1	0.665
APTT	30.3 ± 4.88	101.4 ± 135.2	0.0001*
TT	19.1 ± 2.79	77 ± 145.15	0.976
Fibrinogen	452.2 ± 128.2	496.7 ± 138.06	0.014*
D-dimer	469 ± 616.77	500.9 ± 598.25	0.623

Table 4. The difference of hemostasis value pre and post-hemodialysis with continuous heparin

Variable	Pre HD (n = 25)	Post-HD (n = 25)	P
Trombosit	199,200 ± 56215.36	207,160 ± 54553.25	0.240
PT	11.9 ± 1.06	12.2 ± 1.06	0.262
INR	0.8 ± 0.08	0.9 ± 0.08	0.262
APTT	30.83 ± 3.19	167.5 ± 180.46	0.0001*
TT	18.8 ± 2.54	139.3 ± 197.87	0.466
Fibrinogen	441.4 ± 101.8	499.8 ± 121	0.0001*
D-dimer	264.8 ± 179.76	549.4 ± 664.22	0.007*

Table 5. The outcome of patients receiving intermittent and continuous heparin during regular hemodialysis

Alive (n=39)			Death (n=11)		
Intermittent	Continuous	p.	Intermittent	Continuous	p.
20 (51.3%)	19 (48.7%)	>0.005	5 (45.5%)	6 (54.5%)	> 0.005

Table 6. Adverse reaction that may be produced by intermittent and continuous heparin during regular hemodialysis

	Intermittent	Continuous
Pulmonary embolization	0	0
Deep vein thrombosis	0	0
Acute coronary syndrome	0	0
Bleeding	0	0
Melena	0	0

So far, there were no adverse reactions found during the study, see Table 6.

Heparin is an anticoagulant that inhibits thrombin action through a co-factor named anti-thrombin III (AT-III).[9] Besides, inhibiting thrombin, heparin also inhibited factor IX, factor XII, factor XI, and therefore it prolonged the intrinsic pathway of coagulation.[10,11] As the APTT reflected the action of the intrinsic pathway of coagulation, not surprisingly the APTT was prolonged as seen in our study. The result that the APTT between intermittent and continuous heparin did not show any statistical difference demonstrated that the inhibition of intermittent heparin on the intrinsic pathway acted similarly with continuous heparin. The effect of the increase of fibrinogen was not affected by both intermittent and continuous heparin showing that the inhibition of thrombin was truly effective. An inflamatory reaction might cause the reason why fibrinogen increased during the HD process which triggered the increase of fibrinogen because that fibrinogen was an acute phase reactant.[12,13]

So far, there was no report regarding D-dimer about the survival outcome of patients undergoing hemodialysis. So far to our knowledge, no study had been performed to clarify the use of heparin administration, in this case, continuous and intermittent heparin treatment. Further information was considered necessary to know whether there was a difference of D-dimer between continuous and intermittent heparin during hemodialysis and to relate to the survival outcome of the patients. This might be important for centers of hospitals were the facility for continuous syringe driver for the use of continuous heparin treatment was not available. In many developing countries heparin was available, but the continuous syringe driver instrumentation was not.

One of the most important findings in this study was that D-dimer during continuous heparin showed a significantly higher value in patients receiving continuous heparin compared to intermittent heparin. The continuous administration of heparin produced a steady state of destruction of X-linked fibrin by plasmin through another pathway. There is evidence that D-dimer value was higher in patients receiving continuous heparin compared to intermittent heparin, but did not show the difference in the survival outcome between alive and death. From a clinical perspective point of view, intermittent heparin was not inferior to continuous heparin. Both methods of heparin treatments also did not show an adverse reaction at all, in other words, the increase of D-dimer in continuous heparin treatment was only a limited increase and did not affect survival as well as did not affect the adverse reaction. Both showed good prevention against possible thrombogenesis during HD process. This data could be used as a fundamental concept that the type of either continuous or intermittent heparin were both similarly good for the hemodialysis process. This may reduce the financial burden of hospitals, especially hospitals in developing countries.

CONCLUSION AND SUGGESTION

Both intermittent and continuous heparin were similarly effective and safe. This study can recommend the use of intermittent heparin over continuous heparin especially in hospitals or centers where continuous syringe driver instrument is not available. The researchers suggest continuing the study to a multicenter with more samples and expand investigation with more factors in hemostasis not only D-dimer.

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REFERENCES

1. Kidney Disease Improving Global Outcome (KDIGO). Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int

2013; 3(1): 1-150
2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, *et al*. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. Plos One, 2016; 11(7): 1-18.
3. Kidney Disease Outcome Quality Initiative (KDOQI). Clinical practice guideline for hemodialysis adequacy. Am J Kidney Dis, 2015; 66(5): 884-930.
4. Ambuhl PM, Wuthrich RP, Korte W, Schmid L, Kraft R. Plasma hypercoagulability in hemodialysis patients: impact of dialysis and anticoagulation. Nephrology Dialysis Transplantation, 1997; 12: 2355-64.
5. Fischer KG. Essential of anticoagulation in hemodialysis. Hemodialysis International, 2007; 11: 178-189.
6. Roy A, Kalra V. Anticoagulation in hemodialysis. Jimsa, 2012; 25(2): 107-9
7. Wardle EN. Anticoagulation for hemodialysis and hemofiltration. Saudi J Kidney Dis Transpl, 2002; 13(1): 40-4.
8. European Renal Association. Prevention of clotting in the hemodialysis patient with normal risk of bleeding. Nephrology Dialysis and Transplantation, 2002; 17: 64-66.
9. Rahajuningsih DS. Patofisiologi trombosis. In: Rahajuningsih DS, editors. Hemostasis dan trombosis. 5th Ed., Jakarta, Badan Penerbit Fakultas Kedokteran Universitas Sumatera Utara, 2012; 76-82.
10. Shlebak A. Pathophysiological aspects of coagulation. In: Hakim NS, Calero R. Hemostasis in surgery. London, Imperial College Press, 2007; 1-90.
11. Pasi KJ. Hemostasis. In: Perry DJ, Pasi KJ. Methods in molecular medicine: hemostasis and thrombosis protocols. Totowa, Humana Press Inc. 1999; 3-21.
12. Ramaprabha P, Bhuvaneswari T, Kumar RA. Coagulation profiles an indicator of vascular hemostatic function in chronic renal failure patients who are on renal dialysis. Scholars Journal of Applied Medical Sciences (SJAMS), 2014; 2(2B): 592-5.
13. Alghytan AK, Alsaeed AH. Hematological changes before and after hemodialysis. Scientific Research and Essays, 2012; 7(4): 490-7.