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THE DIFFERENCES VALUE OF P-LCR, THE Β-THROMBOGLOBULIN LEVEL, THE FIBRIN DEGRADATION PRODUCTS LEVEL IN PRE AND POST-HEMODIALYSIS

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ABSTRACT

Hemostasis disorders in End Stage Renal Disease (ESRD) might be due to uremia syndrome which causing platelet dysfunction. This condition was worsened by chronic hemodialysis which affected the biologic compound degranulation of thrombogenic β-thromboglobulin causing morphological changes of platelets which could be evaluated by using the value of Platelet Large Cell Ratio (P-LCR) and triggering fibrinolysis hyperactivation which increased the Fibrin Degradation Products (FDP) level. The sequence of this mechanism happened continuously. The platelet index evaluation could decide the prognosis after hemodialysis, in addition to monitoring creatinine levels. This study aimed to prove the difference between P-LCR, β-thromboglobulin level, FDP level and creatinine level between pre and post-hemodialysis. The design of this study was observational analytical. Forty-five samples were examined by complete blood count examination using flowcytometry method, the level of β-TG examination by ELISA method, the level of FDP examination by the immunoturbidimetric method and the level of creatinine examination by enzymatic method. The statistical analysis used the Wilcoxon test. It was found that the value of P-LCR in ESRD pre-hemodialysis was higher than in post-hemodialysis with the median 26.8 fl and 25.4 fl, the β- thromboglobulin level increased in post-hemodialysis compared to pre-hemodialysis (median 200.88 pg/mL and 313.48pg/mL), the FDP level was higher in post-hemodialysis compared to pre-hemodialysis, (median 1.15 µg/mL and 1.7µg/mL), the creatinine level was lower in post-hemodialysis compared to pre-hemodialysis, (median 13.04 mg/dL and 4.56 mg/dL). Therefore, the statistical value was $p<0.01$. There were significant differences in P-LCR-value, β-thromboglobulin level, fibrin degradation products level and creatinine level between pre and post-hemodialysis.

Key words: P-LCR, β-thromboglobulin, fibrin degradation products, hemodialysis

INTRODUCTION

One of the problems in patients with hemodialysis is associated with ESRD prothrombotic status which can evolve into more severe stages in many cases as well as manifestations of bleeding (bleeding diathesis).[1] Uremia syndrome which occurs in ESRD can cause platelet dysfunction, this condition is exacerbated by the hemodialysis procedure affecting platelet membrane. Repeat on platelet activation, and coagulation factors have resulted in the occurrence of hypercoagulability. Platelets are activated continuously and platelet morphology changes initially, to swelling due to extrusion of filopodia and triggering the release of α-granules containing biological thrombogenic compounds including growth factors and mediators of adhesion aggregation, such as β-thromboglobulin (β-TG), platelet factor 4 (PF4), platelet-derived growth factor (PDGF), von Willebrand factor (vWF) and fibrinogen.[2-4] Marianne *et al.* n research stated that there was an increased β-TG at 15 minutes after starting hemodialysis showing the platelet activation process as an initial activation process of coagulation during hemodialysis. Further, it was possibly causing platelet adhesion and aggregation of platelets as passed through the membrane dialyzer. Hemodialysis induced a hypercoagulable condition which caused side effects such as thrombosis.[5-8]

Hematology examination was required to determine the presence of platelet activation, but in fact, the complete blood count parameter so far has not been used optimally to predict the progression of a disease, mainly associated with prothrombotic status in patients undergoing hemodialysis. Changes in the size and volume of platelets in the degranulation mechanism can be evaluated microscopically and by automated hematology analyzer using Platelet Large Cell Ratio (P-LCR) parameter.[5,8,9] P-LCR is the ratio between the number of large -sized platelets 12-30 fl (PLCC) by the total number of platelets (TC).[9-11] An increase of the value of P-LCR on ESRD indicated an increase in the number and size of varied pseudopodia, or large young platelets, but unfortunately, until now the parameter P-LCR has not been used.[11,12] Hypereactivity of platelets caused by hemodialysis affect primary hemostasis, secondary or fibrinolysis, but also increase the risk of bleeding and thrombosis, thus increasing morbidity and mortality. Plasmin fibrinolysis process aimed to destroy .

excessive fibrin clots by fibrinolysis process.[13,14] Rehealing, the first thing that happens is fibrinogen or fibrin degradation by plasmin to Fibrin Degradation Products (FDP).[14] Malyszko *et al.* and Mortberg *et al.* in a research found a high concentrations of fibrinogen, D-dimer, thrombin-antithrombin complex, factor VII, vWF, trombomodulin, and PAI-1 (Plasminogen Activating Inhibitor-1) in plasma of ESRD patients.[15,16] Prevention of hemostasis function disorders have been studied extending the lifetime of the ESRD patient in varying conditions. Therefore, it is necessary to investigate thrombosis initial marker in patients undergoing hemodialysis at a cost of more simple.[2,16,17]

This study aimed to prove the difference between P-LCR, β-thromboglobulin level, FDP level and creatinine level between pre and post-hemodialysis.

METHODS

Samples from ESRD patients undergoing hemodialysis in the Hemodialysis Unit Telogorejo Hospital, Semarang between October --November 2016 that met the inclusion criteria. The inclusion criteria as follows: patients ESRD Age> 18 years, Complete Blood Count (CBC), analysis of renal function, examination of coagulation, normal liver function and be willing to participate in the study by signing an informed consent. While the exclusion criteria were Heparin-Induced Thrombocytopenia (HIT) and abnormal platelet count of less/more than 150-400.103/µL.

Data were obtained through history, physical examination, laboratory examination and interview questionnaire. Complete blood count was done using a flowcytometry method Sysmex XN-1000, the level of β-TG by ELISA method, FDP levels by turbidimetry immunoassay method and examination of creatinine levels using enzymatic methods. All four tests were conducted on pre and post-hemodialysis.

Data obtained underwent a descriptive analysis (mean, median, standard deviation), then were tested for normality using Saphiro Wilk test. The test results of Shapiro Wilk normality of the data showed that the values of P-LCR, β- thromboglobulin, FDP levels and creatinine levels were not normally distributed, so the data was analyzed by non-parametric Wilcoxon test for pre and post-hemodialysis. Differences were considered significant if was p <0.05.

Research permit of Ethical Clearance was obtained from the Research Ethics Committee Telogorejo Hospital - Semarang No. 19 463 / TU.710 / DIR / K / 2016, and from the Medical Ethics Committee of the Faculty of Medicine Diponegoro No. 932 / EC / FK-RSDK / IX / 2016.

RESULT AND DISCUSSION

Consecutive sampling was collected from 37 patients undergoing hemodialysis who met the inclusion criteria. Each research subject underwent examination for CBC, creatinine levels, levels of β-TG, and FDP levels. End-stage renal disease patients undergoing hemodialysis criteria were obtained from medical records and interviews using guidelines questionnaires which were distributed to the respondents. Characteristics of the results obtained can be seen in the Table 1.

Table 1. Data characteristics of the study subjects (n = 37)

Variable	Total (n (%))	Mean ± SD	Median (min-maks)
Age (year)	-	51.0 ± 4.07	49 (30-80)
Gender			
Male	22 (59.46%)	-	-
Female	15 (40.54%)	-	-
Δ weight (kg)	-	2.53±1.08	2.25(0.5-5)
UF goal (mL)	-	3121,62 ± 990,62	3000 (1000-5000)
QB(mL/menit)	-	194,59 ± 16,8	200 (150-225)
QD(mL/menit)	-	500 ± 0.0	500
Heparin(UI/mL)	-	878,38 ± 225,321	1000 (250 – 1000)
Ureum pre (mg/dL)	37	180,919±56,415	180 (13-348)
Post (mg/dL)	37	64.703±25.31	61(27-137)

Δ B = weight difference before HD - after HD; Goal = fluid ultrafiltration UF

QB = Quick Blood = blood flow; QD = Quick dialysate = dialysate flow

Table 1 shows the mean age of study subjects was 51.0 ± 4.07 years, the youngest is 30 years old and the oldest 80 years old. Gender research subjects mostly male 22 (59.46%) and 15 female subjects (40.54%).

The mean difference in weight pre-post hemodialysis (Δ B) was 2.53 ± 1.08 kg with BB Δ lowest was 0.5 kg and the highest is 5 kg.

The mean goal ultrafiltration (UF Goal) 3121.62 ± 990.62 mL with the lowest value of the UF goal top 1000 mL and 5000 mL. The mean value of QB 194.59 ± 16.8 mL/min with the lowest QB value of 150 mL/min and the highest 225 mL/min. Values entirely QD 500 mL/min. Average heparin used was 878.38 ± 225.321 UI/mL with the lowest amount of heparin 250 UI/mL and the highest 1000 UI/ mL.

The mean pre-hemodialysis urea was 180.919 ± 56.415 mg/dL with the lowest value of 13 mg/dL and the highest of 348 mg/dL, while the average post-hemodialysis urea value showed 64.703 ± 25.31 mg/dL with the lowest levels of 27 mg/dL and the highest levels of 137 mg/dL. The characteristics of each variable in the study described in Table 2.

Values of P-LCR in pre-hemodialysis were significantly higher than post-hemodialysis (p = 0.006). This finding showed a decrease in the value of the P-LCR post- hemodialysis. Examination β-TG levels in pre-PGTA hemodialysis were significantly lower compared

Table 2. Comparison of P-LCR, β- TG levels on pre- and post-hemodialysis (n = 37)

Parameter	Pre HD	Post HD	p
P-LCR (fl)	26.8 (17 – 44.8)	25.4 (18- 40.7)	0.006*
β- TG(ng/mL)	200,88 (102,3 – 434,96)	313,48 (113617 -1116,5)	0.001*
FDP(µg/mL)	1.15 (0.41 – 7.33)	1.7 (0.25 – 6.55)	0.001*
Creatinin (mg/dL)	13.04 (5.33 – 20.7)	4.56 (2.19 – 14.59)	0.001*

Wilcoxon test, * = no significant difference

to pre-hemodialysis.

Distribution of research results was shown in the four parameter box displayed on the graph plots.

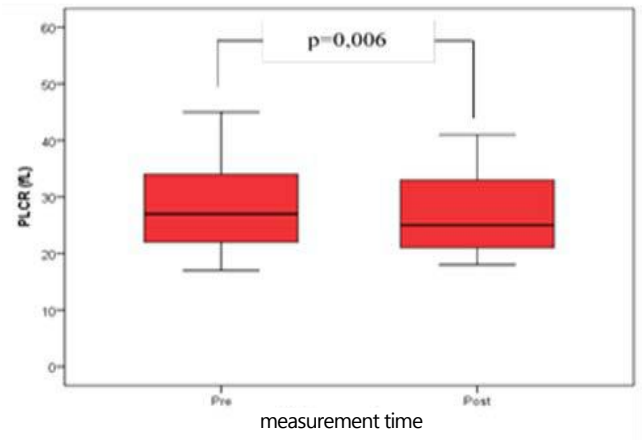

Figure 1. Box plot P-LCR-value in pre and post-hemodialysis

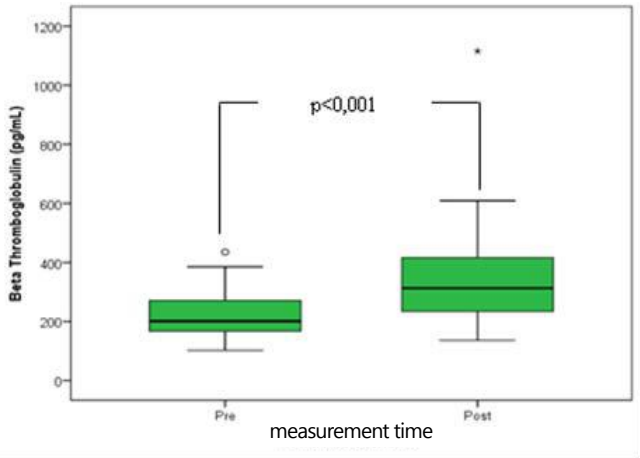

Figure 2. Box plot β- TG levels in pre and post-hemodialysis

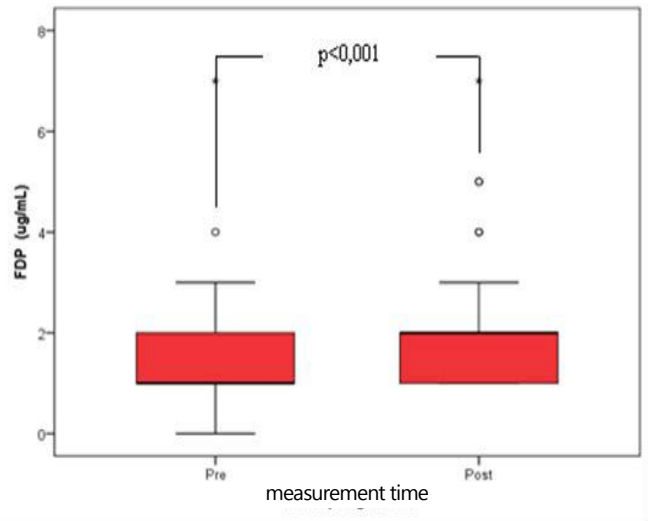

Figure 3. Box plot FDP levels in pre and post-hemodialysis

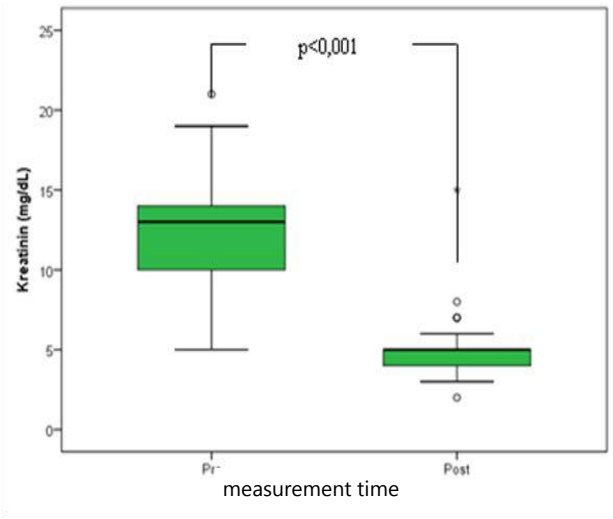

Figure 4. Box plot kreatinin levels in pre and post-hemodialysis

The results showed a decrease in the size of platelet volume; this was indicated by the value of the P-LCR between pre-hemodialysis having a higher value than post-hemodialysis with a median of 26.8 fl in pre-hemodialysis and 25.4 fl in post-hemodialysis. The results were consistent with the theory and previous research suggesting that changes in the size and volume of platelets in platelet degranulation mechanisms can be evaluated microscopically and by automated hematology analyzer using platelet parameters indexes, especially P-LCR.[18,19] Platelets decline in the index was due to the process of hemodialysis, caused platelet activation that swells at the beginning of the degranulation mechanism and further secreting derivate α and dense granules, eventually becoming a flat shape/degranulated platelets. This process led to the interference of the ratio degranulated reticulated and peripheral blood platelets as well as affecting P-LCR as a marker for activated platelets resulting decreased in value of the P-LCR.5,[18-20] The parameters P-LCR can be used to predict the progression of a disease associated with a prothrombotic status of ESRD patients undergoing hemodialysis.[11,19]

The results of this study revealed that a there was an increased β- TG levels in post-hemodialysis compared to pre-hemodialysis, β- TG levels between pre- and post-hemodialysis obtained median values of (200.88 vs. 313.48) ng/mL. Statistical test results in β- TG between the pre, and post-hemodialysis showed a significant difference (p = 0.000). This was consistent with our hypotheses that there was a difference between β-TG levels pre and post-hemodialysis.

Uremia syndrome which occurs in ESRD can cause platelet dysfunction, where hemodialysis procedure affecting the platelet membrane exacerbated the condition. Repeated platelet activation and coagulation factors have resulted in the occurrence of hypercoagulability. Platelets are activated continuously be hyperreactive, platelets which will undergo morphological changes, triggering the release of α granules containing biological thrombogenic mediators compounds such as

growth factors and adhesion aggregation, β-TG, PF4, PDGF, vWF, and fibrinogen.[3,4] Result of β –TG levels in pre and post-hemodialysis which show statistically significant differences more often and the longer the process of hemodialysis result in a hypercoagulable state which can cause thrombosis side effects.[4,6-8]

Examination results of Fibrinogen Degradation Product (FDP) levels were higher in the post-hemodialysis compared with pre hemodialysis. FDP levels between pre and post-hemodialysis showed a median value of (1.15 vs 1.7) pg/ mL. Statistical test results of FDP levels in pre and post-hemodialysis showed a significant difference (p = 0.000). The results were consistent with our hypotheses that there are different levels of FDP between pre and post-hemodialysis with post-hemodialysis FDP levels higher than the pre-hemodialysis.

The results were consistent with the pathophysiology wherein fibrinolysis process aimed to destroy excessive fibrin clot by fibrinolysis process.[13,14] In rehealing, the first thing that happens is fibrinogen or fibrin degradation by plasmin into FDP.[14] positive feedback mechanism in the process of clot lysis rehealing normally is the breakdown of fibrin/fibrinogen by plasmin formed FDP with D-dimer as an end-product. Excessive fibrinolytic activity due to chronic hemodialysis resulted in increasing levels of FDP, D-dimer and hypofibrinogenemia.[1,16,17,21] According to Malyszko *et al.*, and Mortberg, *et al.*, in their research found high concentrations of fibrinogen, D-dimer, thrombin -antithrombin complex, factor VII, vWF, thrombomodulin, and PAI-1 in plasma of ESRD patients.[15] Research on FDP as a marker of fibrinolytic activity in various clinical manifestations is still rare.[2,16] Hyperactive platelets caused by hemodialysis can lead to bleeding and thrombosis thus increasing morbidity and mortality. Prevention of hemostasis disorders is expected to extend the life of people with ESRD, so the presence of hypercoagulable markers of thrombosis in patients with uremia is warranted.[2,17] Test results showed that creatinine levels were lower in post-hemodialysis compared to pre-hemodialysis. Creatinine levels between pre and post-hemodialysis showed median value of (13:04 vs. 4.56) mg/dL. Statistical test results of creatinine levels between pre and post-hemodialysis showed that there was a significant difference (p = 0.000). This was consistent with our hypotheses that there was a difference between creatinine levels pre and post-hemodialysis. Creatinine was used as a parameter of renal dysfunction and ratings specified in determining the glomerular filtration rate because of the nature of which can be filtered creatinine. [22-25]

This study did not examine the parameters URR or LFG as an indicator of the success of hemodialysis, therefore further research is still needed so that it can be the cornerstone of determining diagnosis, evaluating disease progression and determining their prognosis. Monitoring of platelet indices in a routine hematological examination is very useful and can be further optimized in assessing the adverse effects of thrombosis due to hemodialysis in order to determine the ESRD prognosis of those undergoing hemodialysis and are expected to reduce mortality and morbidity.

CONCLUSION AND SUGESTION

It can be concluded that there are significant differences in P-LCR, β-TG, FDP, and creatinine values between pre and post-hemodialysis.

Further research is still needed concerning the P-LCR, β-TG, and other coagulation parameters as prognosis of the success of hemodialysis.

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