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Correlation of Plasma Iron Profile and Intradialytic Hypotension in Hemodialysis Patients

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Abstract: Intradialytic hypotension (IDH) has been a common complication which should be aware of, in hemodialysis procedure. Its pathogenesis is multifactorial, and severe anemia is considered as one of the most notable risk factors on IDH. This study aimed to evaluate the correlation between plasma iron profile and intradialytic hypotension in hemodialysis patients. This was an analytical and retrospective study using medical records of hemodialysis patients at Prof. Dr. R. D. Kandou Hospital, Manado from January to May 2022. Sampling was conducted through consecutive sampling method, on available records. Patients with CKD grade 5 which undergoes routine HD twice a week for >3 weeks, aged 18-60 years old were included, while subjects with sepsis, malignancy, autoimmune disease, crisis hypertension, and unstable congestive heart failure were excluded for further studies. The details on iron profile and blood pressure measurement were then extracted, which then analyzed with descriptive analysis and Pearson correlation using IBM SPSS Statistics 26.0. The results obtained a total of 35 patients; 57.1% were male. The Pearson correlation analysis on all variables reported several notable significant results, with a correlation between iron profile and blood pressure measurement were seen in TIBC and systole pre- and post-procedure (-.496 and -.611 respectively) with strong negative relationship; and serum ferritin value with systole post-procedure (.373) implying moderate positive relationship. The results suggested that the increase of ferritin value and decrease of TIBC value were correlated with the increase of systole blood pressure. Meanwhile, the TIBC had a strong positive correlation with systolic changes (.473) meanwhile serum iron had a moderate negative correlation with diastolic changes (-.365). In conclusion, there is a significant correlation between iron profile and changes in blood pressure, with higher iron profile value (lower TIBC) is positively correlated with the increase of both systole and diastole measurement; also negatively correlated with the reduction of blood pressure in hemodialysis patients
Keywords: iron; ferritin; intradialytic hypotension; hemodialysis; transferrin; total iron binding capacity

INTRODUCTION

Hemodialysis has been a cornerstone of treatment modality of chronic kidney disease, however its importance does not foreclose the risk and adverse reaction it imposes. Ever since the practice of hemodialysis started, intradialytic hypotension (IDH) has been a widely-known, treatment-related, and often distressful complication found in patients undergoing the procedure.[1] National Kidney Foundation Kidney Disease Quality Outcomes Inititative has defined IDH as a reduction in systolic blood pressure of 20 mmHg during dialysis or reduction in mean arterial pressure that occurs with common related symptoms, such as yawning, sighing, nausea, vomiting, abdominal discomfort, muscle cramps, restlessness, anxiety, or light-headedness. Its prevalence in the US is 25% among patients undergoing hemodialysis. This IDH has been associated with increased mortality risk, hospitalization, as well as cardiovascular morbidity.[2]

The multifactorial and complex nature of IDH is making the establishment of disease pathogenesis difficult. Hypovolemic stress and thermal stress impose risks of initiating cascade of IDH occurrence. Combination of declined blood volume, impaired vascular resistance and venous tone caused by reduced cardiac reserve, other comorbidities, all contributes to the manifestation of IDH. Untreated IDH can lead to organ damage mediated by tissue ischemia. This process can be accelerated when comorbid condition is pre-existing in the patient. Pre-existing cardiac failure or autonomous neuropathy might decrease the cardiac output even more, therefore, accelerating the manifestation of IDH. Comorbidities like macro- and microvascular diseases might worsen the outcome of IDH occurrence.[3]

As a common complication of hemodialysis, IDH has several risk factors, including: diabetes mellitus, cardiovascular diseases, poor nutritional status, hypoalbuminemia, autonomic dysfunction, age above 65 years, systolic blood pressure <100 mmHg, and severe anemia. Traditionally, among patients with chronic kidney disease (CKD), IDH is more prevalent in patients with severe anemia.[4]

Anemia is a reduction in hemoglobin (Hb) or hematocrit (HCT) or red blood cell (RBC) count. Whereas anemia can be caused by multiple kinds of etiologies – including blood loss, erythropoietin deficiency, hemolysis, and coagulation abnormalities –, iron deficiency is one of the most common cause of anemia in patient with chronic kidney disease or kidney failure. Laboratory evaluation is important in identifying anemia. Its modality varies from hematoscopy to iron profile analysis. Diagnostic iron studies for iron deficiency anemia consists of low serum iron (<7.1 µg/l), low serum ferritin (storage form of iron) (<30 ng/l), low transferrin saturation (<15%), and high total iron-binding capacity (>13.1 µmol/l).[5] Due to the high prevalence of IDH in patients with severe anemia, this study aimed to investigates the correlation between IDH occurrence and iron profile in patients undergoing hemodialysis.

METHODS

This is an analytical and retrospective study. Data were searched in medical records of hemodialysis patients. Sample collection was done by consecutive sampling, which included all patients with intradialytic hypotension undergoing routine hemodialysis at Prof. Dr. R. D. Kandou Hosppital, Manado. A minimal sample of 30 patients was then calculated to fulfil the analysis of this study. Data collected for this study included demographics (sex, age), iron profiles (serum iron, total iron binding capacity/TIBC, serum transferrin, ferritin), and blood pressure (pre- and post- systole and diastole). The inclusion criteria were, as follows: patients with stage 5 CKD undergoing routine hemodialysis twice a week for ≥3 months; men or women; age 18-60 years old; and willing to participate in this study and signing the informed consent form. Meanwhile, the exclusion criteria were: patients with sepsis; malignancy; history of autoimmune disease; hypertension crisis; and unstable congestive heart failure.

Data collected were pooled and analyzed using IBM SPSS version 28.0 software. Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to test the normality. Descriptive analysis and Pearson correlation were performed to all variables including patient's demographic, iron profile details and blood pressure measurement.

RESULTS

A total of 35 data from patients enrolled at Prof. Dr. R. D. Kandou Hospital, Manado from January to May 2022 were included in data analyses. Majority (57.1%) of them were male with sex ratio of 1.33:1. The mean age was 53.17±13,411 years old.

Iron profile results were as follows: serum iron: 71.2 ±40.268 µg/dL; total iron binding capacity: 208.46±4.595 mcg/dL; serum transferrin: 35.77±20.85 %; serum ferritin 744.66± 668.06 µg/dL. From these results, the mean of serum ferritin was considered very high (744.66 µg/dL). Other iron profile results were varied.

There were also changes in systole and diastole blood pressure between pre- and post-procedure, with mean respective change of 29.21±4.74 and 16.35±11.55. Sample demographic, iron profile, and blood pressure result were shown in Table 1.

Several notable results were found to be significant after Pearson correlation analysis had been run. Correlation with strong negative relationship was seen in correlation between TIBC and systole pre- and post-procedure (respectively r: -0.496 and r: -0.611; p-value <0.01). Positive relationship was shown in correlation of serum ferritin and pre- (r: 0.479; p-value<0.01) and post-procedure systole (r: 0.373; p-value <0.05). The result also implied strong positive relationship of TIBC level compared to changes of systolic blood pressure (r: 0.473; p-value <0.01), as well as moderate negative correlation of serum iron when compared to changes of diastolic blood pressure (r: -0.365; p-value<0.05)

The results suggested that increase of systolic blood pressure was directly proportional to serum ferritin level, and inversely proportional to serum TIBC value. Pearson correlation analysis was shown in Table 2.

DISCUSSION

Intradialytic hypotension is a common complication in patients with CKD and kidney failure undergoing hemodialysis. One of its main risk factors is severe anemia. Iron panel test, which consist of measurement of serum iron, ferritin, transferrin, TIBC, and transferrin saturation, can predict the diagnosis of various types anemia, with additional Hb and MCV test. In severe anemia due to deficiency of iron, it manifests as decreased serum iron and serum ferritin, and normal to increased TIBC. However, when it comes to anemia due to inflammatory disease, TIBC is expected to be normal or decreased, and serum ferritin is expected to be normal or increased.

In this study, iron profile, particularly TIBC, have strong correlation with blood pressure changes in patients undergoing hemodialysis procedure. TIBC is negatively correlated with the both pre- and post-dialysis systolic blood pressure measurement. TIBC is also positively correlated with decrease of systolic blood pressure changes in patients undergoing hemodialysis.

A study done by Okoye et al[5] in African population concluded that anemia, as well as other traditional risk factors – such as old age -- , was not significantly associated with the occurrence of IDH.[4] This result was further explained in a study done by Park et al,[5] where its findings concluded that the level of TIBC is constant among various result of changes in systolic blood pressure. Serum ferritin value also seemed to fluctuates among different result of systolic blood pressure shift. From these studies, the result of iron profile might not be significantly related with the prevalence of IDH.

However, it is known that prescription of iron supplementation – namely iron citrate, iron sacharrate, or iron sucrose – to patients with dialysis-associated anemia has efficacious result, and its safety has been evaluated. This practice has been a norm since 50 years ago in the United States. Its administration were proven to significantly increase serum iron, serum transferrin saturation, and serum ferritin levels; as well as significantly decrease TIBC.[6-7] Regarding its effect to intradialytic blood pressure, the drop in blood pressure during hemodialysis was more pronounced when iron was not administered.[8]

In correlation of iron profile with hypertension itself, the results were quite consistent. A cohort study done among middle-aged men exhibited that serum ferritin is positively associated

with occurrence of hypertension.[9] Other cross-sectional study suggested also that prevalence of hypertension is positively associated with the level of serum ferritin.[10] These findings suggest that iron metabolism dysregulation metabolism as an notable risk factor for essential hypertension.[9] The reason behind it is in patient with iron overload display significantly greater sympathetic activation of blood pressure. This iron overload is shown by the level of serum ferritin, serum transferrin, hepatic iron content, and detection of hepatic steatosis.[11]

On the other hand, hemodynamic instability during hemodialysis is caused by rapid rise ultrafiltration, in which compensatory cardiovascular responses – such as vasoconstriction and increasing cardiac output – is failed to elicit, leading to a drop of blood pressure.[12] In this pathophysiology, ultrafiltration rates have emerged as an important and potentially modifiable risk factor. Ultrafiltration rates correlates more with frequent cardiac wall abnormalities, but consequently, initial approach to prevent IDH is the reduction of ultrafiltration rate. In this cascade, the role of iron administration relies on iron potency to elevate vascular tone, therefore reducing ultrafiltration rate, hence raising blood pressure.[8]

Traditionally, prediction of IDH occurrence is determined by looking at pre-existing patient characteristics such as older age, comorbidities like diabetes and longer dialysis period, which patients are known to be prone to IDH. This study is important, considering the intermittent nature of dialysis procedure making IDH can likely not be completely prevented due to the intermittent nature of dialysis procedure. Findings in the study can further provide reference for future recommendation to screen severe anemia by taking serum iron profile prior and after hemodialysis.

This study is not without limitation, retrospective nature of this study could not directly determine the comparison between various iron serum level on the incidence of IDH. Limited scope of sample size and population also become setback in producing conclusive result, as well as increasing the margin of error, which can render the study meaningless. Severe anemia itself have multiple etiology and mechanism, therefore measurement of iron ferritin alone does not constitute the occurrence of severe anemia.

CONCLUSION

Iron profile, particularly TIBC, have a strong correlation with blood pressure changes in patients undergoing hemodialysis procedure. For further study, it is recommended to include more samples from various centres, preferably including more branches, other than iron profile, that might reflect the manifestation of severe anemia. Replication of this study is encouraged, so that, iron profile as a determinant of hemodynamic stability in pre-hemodialysis patients can be more established.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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Table 1. Included samples' characteristics

Samples' characteristics	**N (%)**	**Minimum**	**Maximum**	**Mean**	**Standard Deviation**
Sex					
Male	20 (57.1)				
Female	15 (42.9)				
Age (yrs)		21	81	53.17	13.41
Serum iron (µg/dL)		23	224	71.23	40.27
TIBC (mcg/dL)		121	354	208.46	54.59
Serum transferrin (%)		10	99	35.77	20.85
Serum ferritin (µg/dL)		31	2000	744.66	668.06
Systole pre (mmHg)		135	170	155.32	10.37
Diastole pre (mmHg)		65	100	80.88	8.91
Systole post (mmHg)		92	135	110.06	11.62
Diastole post (mmHg)		57	96	67.03	7.49
% Systole changes		20.59	37.94	29.21	4.74
% Diastole changes		-9.23	34.83	16.35	11.55

Table 2. Correlation (r-value) of extracted variables on the incidence of intradialytic hypotention (Pearson correlation analysis)

Samples' characteristics	Age	Iron	TIBC	Trans-ferrin	Ferritin	Systole Pre	Diastole Pre	Systole Post	Diastole Post	% SC	% DC
Age	1	.047	.014	.069	-.086	.063	.301	.056	-.193	-.027	.388*
Iron	.047	1	.078	.903**	.530**	.117	-.217	-.068	.193	.225	-.365*
TIBC	.014	.078	1	-.300	-.276	-.496**	-.084	-.611**	-.066	.473**	.005
Transferrin	.069	.903**	-.300	1	.620**	.306	-.122	.164	.172	.050	-.278
Ferritin	-.086	.530**	-.276	.620**	1	.479**	.176	.373*	.329	.-0.97	-.126
Systole Pre	.063	.117	-.496**	.306	.479**	1	.347*	.782**	.436**	-.212	-.089
Diastole Pre	.301	-.217	-.084	-.122	.176	.347*	1	.446**	.254	-.339*	.632**
Systole Post	.056	-.068	-.611**	.164	.373*	.782**	.446**	1	.463**	-.775**	-.004
Diastole Post	-.193	.193	-.066	.172	.329	.436**	.254	.463**	1	-.281	-.579**
% SC	-.027	.201	.473**	.050	-.097	-.212	-.339*	-.775*	-.281	1	-.079
% DC	.388*	-.365*	.005	-.278	-.126	-.089	.632**	-.004	-.579**	-.079	1

TIBC: Total Iron Binding Capacity; %SC: Systole Changes; %DC: Diastole Changes
*Significant (p-value <0.05); **Significant (p-value <0.01)