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The effects of long-term haemodialysis on red cell distribution width, haemoglobin, fibrinogen, D-dimer and survival outcome

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Abstract

Background: Haemodialysis has become an increasingly safe and well-tolerated long-term maintenance therapy for end-stage renal disease. However, the highest mortality rate was found within the six months of initiating dialysis commonly due to cardiovascular disease. The aim of the study is to determine the effects of long-term haemodialysis on red cell distribution width, haemoglobin, fibrinogen, D-dimer, urea reduction and survival outcome.

Materials and Methods: 50 patients on long-term haemodialysis were recruited (males n=30, females n=20). Their mean age was 50.4 ± 12.4 years ranging between 18 and 68 years old. Blood sampling was performed before and after haemodialysis; haemoglobin, RDW, fibrinogen, D-dimer and urea reduction percentage were determined.

Results and Discussion: No statistically significant differences in haemoglobin, RDW and D-dimer before and after haemodialysis except for elevated fibrinogen (P=0.04) and urea reduction percentage (P=<0.001), similarly no significant differences between those who died and still living were found. Wide variations in the parameters studied could account for these differences. Eleven patients died (22%) and ten (91%) within 18 months and 5.5 years and the last one (9%) after 8.75 years of haemodialysis.

Conclusion: Wide variations in the parameters studied were seen. No clear indication as to which markers are responsible for survival outcome and may be other unknown factors are involved.

Keywords: long-term haemodialysis, survival outcome

1. Introduction

Patients with chronic kidney disease (CKD) generally experience loss of kidney function and are at risk of end-stage renal disease. In CKD stage 5 renal function must be replaced by dialysis or kidney transplantation. Haemodialysis (HD) has become an increasingly safe and well-tolerated therapy for patients with end-stage renal disease (ESRD), however, life expectancy is shorter than that of the general population with similar demographics [1]. Haemodialysis has become the long-term maintenance therapy with the highest mortality rate found within the first six months of initiating dialysis and most commonly due to cardiovascular disease where mortality is 10-12 times higher [2-4].

Red cell distribution width (RDW) is a quantitative marker of the variability in the size of erythrocytes or volume [5]. Elevated RDW suggests increased size variation of red blood cells indicating altered life span or dysfunction [6, 7]. It has been reported to be a predictor of mortality in the general population and in CKD patients on HD [8, 9] including acute and chronic heart failure [10-12], acute pulmonary embolism [13], myocardial infarction [14] and a predictor of cardiovascular event in a 3-year follow up [12]. Anaemia occurs early in the development of kidney disease which worsens with declining kidney function. CKD and anaemia are well known risk factors for cardiovascular events and mortality. Anaemia of CKD in most patients were normochromic normocytic red blood cells and principally due to reduced renal erythropoietin production and to a lesser extent to shortened red blood cell survival and iron deficiency. Moreover, current data concerning the effective management of anaemia in CKD patients is inadequate [15]. Fibrinogen, an acute phase reactant protein rises in response to systemic inflammation, tissue injury and elevated levels seen in chronic kidney disease [16]. The role of D-dimer assays in the diagnosis of suspected deep vein thrombosis (DVT) and a useful tool in the management of patients with DVT and pulmonary embolism has been extensively studied [17, 18]. It is a marker for hypercoagulability and has been shown to have a high sensitivity and high negative-predictive value for DVT exclusion [19]. However, almost all patients with impaired renal function had elevated D-dimer irrespective of the presence of pulmonary embolism has been reported [20]. Elevated D-dimer and fibrinogen levels in CDK patients are high risk factors for thromboembolic events [2, 21].

The objective of the study is to determine the effects of long-term haemodialysis on red cell distribution width,

haemoglobin, fibrinogen, D-dimer, urea reduction percentage and survival outcome.

2. Materials and Methods

The study received ethical approval from the Ethical Committee for Medical Research, University of North Sumatera/Haj Adam Malik Hospital (168/TGL/KEPK FK, USU- RSUP HAM/2017). Informed Consent was obtained from all patients involved in the study.

Subjects

The recruitment of patients was carried out in the Division of Nephrology, Haemodialysis Unit, Haj Adam Malik Hospital, and Medan. Fifty chronic kidney disease patients (Males n=30; females n=20) with Stage 5 disease who have undergone haemodialysis for between one year and nine years were recruited after obtaining their Informed Consent. Their mean age was 50.4 ±12.4 years and ranged between 18 to 68 years old.

The National Health Insurance Policy for patients receiving regular haemodialysis (HD) allows only twice a week dialysis. A loading dose of bolus heparin of 1500 to 2000 IU through the arterial line for all patients receiving HD. 25 patients received heparin dose of 1000 IU/hour through a continuous syringe driver and the other 25 patients had intermittent injection of 1000 IU/hour through the arterial line.

Inclusion Criteria

Patients between 18 and 65 years of age and had received recombinant human erythropoietin (rhuEPO) of more than 3 months, ferritin level >100 mg/dL and or transferrin saturation index (TSI) >20%.

Exclusion Criteria

Patients below 18 years and above 65 years and with no history of thalassaemia.

Blood sampling was performed 5 to 10 minutes before the start of HD and again about 30 minutes after completion of HD. From a clean venepuncture about 10 mL of blood drawn from the median vein with 3 mL for the EDTA and 3 mL into 3.8% tri-sodium citrate vacutainer and the remainder into the plain vacutainer for serum collection. Citrated blood was spun at 2500g for 15 minutes and the plasma aliquoted.

Laboratory investigation

EDTA blood was used to determine haemoglobin and red cell distribution width (RDW) in the Sysmex XN1000 analyser (Kobe, Japan). Citrated plasma was used for determination of fibrinogen (TEClot FIB, Germany) and D-dimer (Blue, D-dimer LC kit, Germany) in the Coatron A6 analyser (TECO Medical Instruments, Germany). Serum urea reduction percentage was also determined and calculated.

Statistical Analysis

The Statistical Package or Social Sciences (SPSS 22 IBM Corp) was used for statistical analysis. The group mean independent t-test was performed to compare before and after haemodialysis. A P-value of <0.05 was considered statistically significant.

3. Results

Characteristics of chronic kidney disease patients on long-term haemodialysis

Fifty patients (males n=30, female n=20) with Stage 5 kidney disease and on long-term haemodialysis were recruited after obtaining their informed consent. Their mean age was 50.4 ± 12.4 years and raged between 18 and 68 years old. The patients were followed-up for 14 months from study. Eleven (22%) patients died between 18 months and 8.75 years of haemodialysis and the remainder is still living past one year and more than eleven years on haemodialysis at time of study. Their characteristics are shown in Table 1.

Haemoglobin, RDW, fibrinogen, D-dimer and urea concentration before and after haemodialysis in chronic kidney disease

There were no statistically significant differences for haemoglobin (P=0.07), RDW (P=0.72) and D-dimer (P=0.15) before and after haemodialysis except for fibrinogen (P=0.04) and urea reduction percentage (P=<0.001). There are wide variations in the parameters studied and could account for this discrepancy (Table 2).

No statistically significant differences were seen in the parameters studied between the patients undergoing haemodialysis who died (n=11) and those still living (n=39) (not shown). Distribution of haemoglobin, RDW, fibrinogen and D-dimer before and after haemodialysis and mortality in chronic kidney disease cohorts.

The distribution of patients to levels of normal and elevated RDW, fibrinogen and D-dimer together with haemoglobin and mortality outcome are shown in Table 3. Twenty-two (44%) patients are still severely anaemic with haemoglobin levels of <10 g/L after haemodialysis and are associated with 5 deaths. A rise of 2% for RDW, fibrinogen (10%) and D-dimer (10%) and mortality rates after haemodialysis are shown (Table 3).

The distribution of haemoglobin, RDW fibrinogen and D-dimer in patients who died after haemodialysis are shown in Figure 1. Mortality in chronic disease patients on long-term haemodialysis. The patients were followed-up for fourteen months. Eleven patients (22%) died in this study between 18 months and 8.75 years after haemodialysis and their cause of death was recorded as myocardial infarction. Between 18 months and 3 years, 5 patients (10%) died and between 4.0 and 5.5 years another 5 died (10%), the last patient (2%) died after undergoing haemodialysis for 8.75 years. Most of the death (91%) in this study died within 18 months and 5.5 years after undergoing haemodialysis. Mortality seems to be nearly evenly distributed in those who died with severe anaemia (n=5, 45.5%) and normal levels for RDW (n=5, 45.5%), fibrinogen (n=4, 36.4%) and D-dimer (n=5, 45.5%) compared to those with higher haemoglobin levels (54.5%) and elevated RDW (32%) fibrinogen (63.6%) and D-dimer (54.5%) (Table 3).

How long is long-term haemodialysis. We mentioned here a living 46-year old male patient who had undergone more than 11 years of haemodialysis. His haemoglobin level after haemodialysis was 14.7g/L, RDW 14.7%, fibrinogen 4.56 g/L and D-dimer 811 ng/mL. Could age and haemoglobin levels be the probable key factors contributing to long-term haemodialysis.

Table 1: Characteristics of chronic kidney disease patients on long-term haemodialysis.

N = 50 Males n = 30; females n = 20
Age: mean 50.4 ±12.4 years; range 18 to 68 years
Diagnosis: (Stage 5 kidney disease)
Hypertensive nephropathy n= 28
Diabetic nephropathy n = 10
Obstructive infective kidney n = 5
Chronic glomerulonephritis n = 3
Chronic pyelonephritis n = 2
Polycystic kidney disease n = 1
Gout associated chronic kidney disease n = 1
Haemodialysis cycles: on-going (twice a week)
12 months to 24 months n = 25
30 months to 48 months n = 18
>60 months n =7
Mortality outcome: n = 11 (22%) between 18 months to 8.75 years of haemodialysis
Still living: n = 39 (78%) past 1 year to 9 years of haemodialysis

Table 2: Haemoglobin, RDW, fibrinogen, D-dimer and urea concentration before and after haemodialysis in chronic kidney disease.

	Before haemodialysis	**After haemodialysis**	***P***
N	**50**	**50**	
Haemoglobin g/dl			
Mean (SD)	93 (1.8)	1024 (2.1)	
Range	6.4 — 14.0	6A — 14.0	0.07
RDW (%)			
Mean (SD)	143 (1.8)	14A (1.8)	
Range	12.4 — 22.9	122 -22.4	32
Fibrinogen g/L			
Mean (SD)	4A7 (Oil)	4.98 (013)	
Range	2.57 — 729	2.54 — 8.01	0.04
D-dimer (ng/mL)			
Mean (SD)	366.9 (46L2)	5282 (625.3)	
Range	66.0 — 2814	38.0 - 2652	0.15
Urea (mg/mL)			
Mean (SD)	1243 (315)	34A (12.3)	
Range	58 — 212	13 - 71	<0.001
Urea Reduction %			
Mean (SD)		722 (8.3)	
Range		(5L4 to 93.9)	

RDW = red cell distribution width

Table 3: Distribution of haemoglobin, RDW, fibrinogen and D-dimer before and after haemodialysis and mortality in chronic kidney disease cohorts

Haemoglobin	**<10 g/L**	**10 – 12.0 g/L**	**> 12.0g/L**
Before HD n	28 (56%)	19 (38%)	3 (6%)
After HD n	22 (44%)	21 (42%)	7 (14%)
Died n	5 (45.5%)	4 (36.4%)	2 (18.1%)
RDW	≤ 15.0%	> 15.0 %	
Before HD n	35 (70%)	15 (30%)	
After HD n	34(68%)	16 (32%)	
Died n	5 (45.5%)	6 (54.5%)	
Fibrinogen	5 4.00 g/L	> 4.00 g/L	
Before HD n	17 (34%)	33 (66%)	
After HD n	12 (24%)	38 (76%)	
Died	4 (36.4%)	7 (63.6%)	
D-dimer	5 500 ng/mL	> 500 ng/mL	
Before HD n	41(82%)	9(18%)	
After HD /1	36 (72%)	14 (28%)	
Died a	5 (45.5%)	6 (54.5%)	

HD= haemodialysis

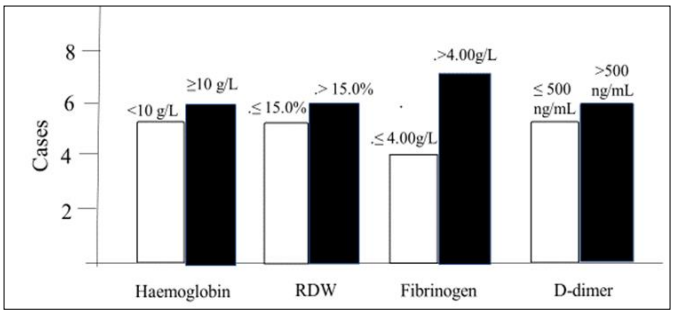

Fig 1: Distribution of haemoglobin, RDW, fibrinogen and D-dimer in patients on long-term haemodialysis who died (n=11).

4. Discussion

Cardiovascular disease is the leading cause of death in end-stage renal disease [2, 22]. Mortality rates were highest in the early dialysis period probably because of the inclusion of patients with poor short-term prognosis and the influence of differences in early dialysis-related medical care. The mortality rates from eleven countries from first day of dialysis to 120 days ranged between 23.8% and 29.3% and the highest rate is within 30 days of dialysis (29.3%) [4]. Our study showed that the first mortality was recorded after 18 months of haemodialysis and 91% of mortality (10/11) occurred at 18 months and 5.5 years of haemodialysis and 9% (1/11) after 8,5 years. Mortality seems to be nearly evenly distributed in both groups of patients with severe anaemia and haemoglobin >10 g/L (45.5% vs 54.5%) similarly for normal and elevated group for RDW and D-dimer and with fibrinogen (36.4% vs 63.6%). Wide variations in the parameters studied showed no significant differences before and after haemodialysis except for fibrinogen levels which showed a further 10% increase from 66% (n=33) before haemodialysis in the elevated fibrinogen group. Fibrinogen and D-dimer levels were shown to be elevated in other studies [2, 20, 21] but we found only 76% of patients having elevated fibrinogen levels and 28% D-dimer, these may be the risk factors for thromboembolic events. High RDW has been shown to be associated with increased risk for cardiovascular events [3-25], only 32% of our patients had elevated levels. Severe anaemia of haemoglobin < 10g/L persist in 44% of our patients after haemodialysis and this is well known risk factor for cardiovascular events and mortality. We could not find any significant differences in the parameters studied between those still living and dead. Urea reduction was significantly reduced in all patients after haemodialysis. Anaemia, RDW and elevated fibrinogen and D-dimer are known markers for thromboembolic risks and cardiovascular events but in long-term haemodialysis these elevated markers are not solely associated with mortality outcome suggesting that there are other markers responsible for mortality and survival outcome in long-term haemodialysis. A case in mind from our study whether age and haemoglobin can contribute to long-term haemodialysis despite the elevated fibrinogen and D-dimer seen.

5. Conclusion

In long-term haemodialysis wide variations in parameters studied were seen. Severe anaemia persists in 44% of patients with increase in RDW (32%), fibrinogen (76%) and D-dimer

(28%) after haemodialysis. Significant urea reduction percentage was seen in all patients. Eleven patients died (22%) from myocardial infarction within 18 months and 5.5 years after haemodialysis and one at 8.5 years. No clear indication as to which markers are responsible for survival outcome and may be other unknown factors are involved

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Conflict of Interest
The authors declared that they have no conflict of interest.

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