Effect of Erythropoietin on Haematological Parameters in Chronic Renal Failure Patients Undergoing Dialysis in Malaysia

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ABSTRACT

Background: **The worldwide rise in the number of patients with chronic renal failure (CRF). Chronic Renal Failure is a major health problem resulting in considerable increase in mortality and morbidity, decreased quality of life and heavy cost of therapies. .**

Objective: **This study aims to evaluate the haematological parameters and iron status during monitoring of Chronic Renal Failure patients and to study the effects of subcutaneously and intravenously administered erythropoietin (EPO) in treating anaemia in Chronic Renal Failure patients.**

Methods: **A retrospective record review study was conducted among the CRF patients treated at Hospital Pulau Pinang between 2005 and 2009. A total of 45 patients were randomly selected by using simple random sampling. The parameters were taken one to two weeks prior to EPO treatment and at 1 month and 3 months after EPO therapy was started. Data analyses were performed by using paired t test and independent t test via SPSS Version. 18.0.0.**

Results: **After one month post-EPO, there was a significant difference of mean serum iron between continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis groups where the mean value of serum iron was higher in CAPD group. After three months post-EPO, there were significant differences of mean white blood cells and serum iron between the two groups.**

Conclusions: **Chronic renal failure patients undergoing dialysis responded to EPO treatment and subcutaneous EPO administration appeared to give more favourable results compared to intravenous EPO.**

KEY WORDS

anaemia, chronic renal failure, dialysis, erythropoietin, haematological parameters, Malaysia

INTRODUCTION

Chronic renal failure (CRF) is a condition in which the kidney function gradually declines and irreversible the destruction of kidney with a serious and also long term medical condition[1)].

The worldwide rise in the number of patients with CRF is a major health problem resulting in considerable increase in mortality and morbidity, decreased quality of life and heavy cost of therapies. Diabetes, hypertension, an older age and obesity are considered to be risk factors assicated with development of CRF[2,3)]. Patients with CRF are often anaemic, have poor haemostasis, and may show leukocyte and platelet function abnormalities[4)].

Anaemia is the most common problem faced in patients with CRF[5)]. Observational studies in haemodialysis patients have found anaemia to be associated with higher mortality in populations in which the vast majority of patients had hemoglobin levels between 6 and 12 g/dl[6-8)]. Associations of anaemia with hospitalization and resource utilization also have been reported[9,10)]

The prevalence of CKD and end-stage renal disease (ESRD) is increasing through the worldwide. The estimated prevalence of CKD in the US was 16.8% while in Asia the prevalence ranged from 12.1% to 17.5%[11-13)].

In Malaysia, the incidence and prevalence of patients with ESRD on dialysis had increased from 88 and 325 per million population (pmp) respectively in 2001 to 170 and 762 per million population respectively in 2009[14)].

The growing number of ESRD places an enormous human, economic and social burden on the healthcare system. In an economic evaluation among Ministry of Health, dialysis centers in Malaysia, the cost

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Table 1. Comparison of mean haematological parameters and iron status between pre and one month after EPO treatment in CAPD group of patients (n = 20)

Variables	Pre-EPO	1 month post-EPO	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	9.73 (1.10)	10.08 (1.58)	0.35 (-1.21, 0.51)	0.85 (19)	0.405
MCV	86.89 (4.67)	90.69 (5.65)	3.80 (1.94, 5.67)	4.27 (19)	< 0.001*
MCHC	32.60 (0.10)	32.33 (1.03)	-0.27 (-0.23, 0.77)	-1.13 (19)	0.269
WBC	7.82 (1.81)	7.02 (5.65)	-0.80 (-0.86, 0.80)	58.6 (19)	0.426
Lymphocyte count	2.01 (0.59)	2.26 (0.73)	0.25 (0.07, 0.51)	2.09 (19)	0.049
Platelet count	283.20 (58.91)	252.40 (39.49)	-30.80 (7.69, 53.91)	-2.78 (19)	0.012*
Ferritin	746.80 (337.24)	651.92 (370.59)	94.90 (28.82, 218.57)	-1.60 (19)	0.125
Serum iron	13.77 (7.64)	13.02 (5.41)	-0.75 (-3.13, 4.63)	-0.40 (19)	0.691
TIBC	41.60 (11.66)	43.63 (7.53)	2.03 (-7.27, 3.19)	0.81 (19)	< 0.001*

[a]Paired *t* test was applied

Table 2. Comparison of mean haematological parameters and iron status between pre and three month after EPO treatment in CAPD group of patients (n = 20)

Variables	Pre-EPO	3 month post-EPO	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	9.73 (1.10)	14.92 (18.62)	5.19 (-3.64, 14.02)	-0.23 (19)	0.234
MCV	86.89 (4.67)	87.68 (14.04)	0.79 (-7.88, 6.29)	0.23 (19)	0.818
MCHC	32.60 (0.10)	31.17 (6.05)	-1.43 (-1.43, 4.22)	-1.07 (19)	0.290
WBC	7.82 (1.81)	7.03 (1.79)	-0.79 (-1.17, 1.70)	-1.82 (19)	0.084
Lymphocyte count	2.01 (0.59)	2.03 (0.55)	-0.20 (-0.23, 0.18)	0.21 (19)	0.840
Platelet count	283.20 (58.91)	230.24 (75.62)	-52.96 (-80.90, -25.01)	-3.96 (19)	0.001*
Ferritin	746.80 (337.24)	625.48 (355.30)	-121.30 (-298.2, 55.6)	-1.43 (19)	0.168
Serum iron	13.77 (7.64)	15.13 (9.70)	1.36 (-7.68, 4.95)	0.45 (19)	0.650
TIBC	41.60 (11.66)	44.57 (9.01)	2.97 (-2.20, 8.15)	1.20 (19)	0.244

[a]Paired *t* test was applied

of dialysis and erythropoietin was RM2,500 per month[15] while compared in the US, the cost of medical care was 1.7 times higher in patients with CKD stage 3 and 2.6 times higher in those with stage 4 CKD compared with controls[16,17].

Many factors have been implicated in its pathogenesis, which include a markedly depressed erythropoiesis due to reduced erythropoietin (EPO) production in the kidney[18]. Recombinant human erythropoietin (rHuEPO) is one of the greatest advances in nephrological practice over the last decades. Before the advent of recombinant human erythropoietin, many patients with renal failure required repeated blood transfusions in order to avoid the symptoms and complications of severe anaemia. Erythropoietin which is produced by recombinant DNA technology in mammalian cell is used in treating anaemia resulting from CRF[19].

Recombinant human erythropoietin is inactivated by acid in the stomach, and therefore needs to be given parenterally. In the early haemodialysis clinical trials, patients were administered intravenous erythropoietin thrice weekly. Subsequently, the intraperitoneal, Subcutaneous and intradermal routes of administration were investigated[20].

Many studies have compared the efficacy and dose requirement of erythropoietin administrated intravenously versus subcutaneously. Most suggest lower dose may be required if the subcutaneous route is used[21]. Considering the practicality of the subcutaneous route, it seems very likely that this is going to become the standard mode of EPO administration.

Regular monitoring of patients physical vital signs as well as monitoring of laboratory parameters such as haematological parameters and iron status are done to evaluate the efficacy of erythropoietin are extremely important.

This study was aimed to evaluate these haematological parameters and iron status during mnitoring of CRF patients, and to study the effects of subcutaneously and intravenously administered erythropoietin (EPO) in treating anaemia in CRF patients.

MATERIALS AND METHODS

A retrospective record review study was conducted among the chronic renal failure patients treated at Hospital Pulau Pinang, Malaysia whose clinical records were available within the time frame between 2005 and 2009. The participants were all chronic renal failure patients on erythropoietin treatment. Only patients who had completed records of all haematological parameters and iron status variables were included in the study. Patients who were given erythropoietin due to cancer or diseases other than CRF were excluded from the study.

The calculation of sample size was performed with requirements for level of significance 0.05 and power of 80% using two means (paired) formula. The predetermined sample size was 45. The data was obtained from patients' clinical records in Nephrology Department from Haemodialysis and Continuous Ambulatory Peritoneal Dialysis (CAPD) units at Hospital Pulau Pinang.

The total number of clinical records of chronic renal failure patients undergoing dialysis in Hospital Pulau Pinang was 237. This consisted of 175 on CAPD and 62 on haemodialysis. The total number of clinical records of patients who were treated with recombinant human erythropoietin was 51 from haemodialysis unit and 148 from CAPD unit. A total of 45 patients who had complete haematological parameter and iron status were randomly selected by using simple random sampling: 20 from CAPD unit and 25 in haemodialysis unit.

Patients on CAPD were treated with recombinant human erythropoietin (EPO) by subcutaneous injections, of doses in the range of 2 000, 4 000, 8 000 and 12 000 IU/mL two to three times weekly. On the other hand, patients on haemodialysis received recombinant human erythropoietin (EPO) by intravenous route with a dose range of 2 000 – 4 000 IU/mL three times weekly.

The clinical records were reviewed by a single researcher and a data collection form was used to record all the information in the clinical records which included age, gender, diagnosis of the patients, type of erythropoietin treatment, and administration of erythropoietin and dose of the erythropoietin given.

The haematological parameters with respective measurement units were also obtained from patients' clinical records which included haemoglobin (HB) g/dL, mean corpuscular volume (MCV) fL, mean corpuscular haemoglobin concentration (MCHC) g/dL, white blood cells (WBC) 10^3/µL, lymphocyte count 10^3/µL, platelet count 10^3/µL, serum iron µmol/L, serum ferritin g/dL and total iron biding capacity (TIBC) µmol/L. However, data for lymphocyte count was unavailable in patients' clinical records, and were not included in the data analysis. These parameters were taken one to two weeks prior to EPO treatment (pre-EPO), and at 1 month and 3 months after EPO therapy was started (post-EPO).

Ethical clearance was obtained from Clinical Research Center of Hospital Pulau Pinang, Research and Medical Research Ethics Committees in the Ministry of Health Malaysia and Research and Ethics Committee of Advanced Medical and Dental Institute, Universiti Sains Malaysia.

Table 3. Comparison of mean haematological parameters and iron status between pre and one month after EPO treatment in haemodialysis group of patients (n = 25)

Variables	Pre-EPO	1 month post-EPO	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	9.34 (1.56)	10.35 (1.54)	1.01 (0.38, 1.65)	3.31 (24)	0.030*
MCV	91.56 (8.46)	91.12 (7.83)	-0.44 (-1.16, 2.05)	-5.69 (24)	0.575
MCHC	31.72 (1.87)	31.49 (2.48)	-0.22 (-0.86, 1.31)	-4.25 (24)	0.675
WBC	8.06 (2.64)	8.51 (5.40)	0.45 (-2.37, 1.47)	0.48 (24)	0.635
Platelet count	226.80 (66.17)	224.16 (64.75)	-2.64 (-16.60, 21.88)	-0.28 (24)	0.779
Ferritin	615.76 (661.52)	596.37 (619.07)	-19.37 (-66.20, 105.01)	-0.46 (24)	0.644
Serum iron	11.40 (7.64)	7.97 (5.07)	-3.43 (-6.06, 0.80)	-2.72 (24)	0.130
TIBC	41.83 (11.25)	39.12 (8.46)	-2.71 (-6.55, 1.12)	-1.48 (24)	0.156

[a]Paired *t* test was applied

Table 4. Comparison of mean haematological parameters and iron status between pre and three month after EPO treatment in haemodialysis group of patients (n = 25)

Variables	Pre-EPO	3 month post-EPO	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	9.34 (1.56)	11.22 (1.45)	1.88 (1.12, 2.65)	5.08 (24)	< 0.001*
MCV	91.56 (8.46)	90.22 (8.47)	-1.34 (-3.11, 0.43)	-1.55 (24)	0.132
MCHC	31.72 (1.87)	31.87 (1.98)	0.15 (-0.76, 0.45)	0.51 (24)	0.612
WBC	8.06 (2.64)	8.57 (2.83)	0.51 (-1.85, 0.82)	0.79 (23)	0.439
Platelet count	226.80 (66.17)	225.12 (61.29)	-1.68 (-16.80, 20.16)	-0.19 (24)	0.853
Ferritin	615.76 (661.52)	592.80 (894.64)	-22.96 (-152.86, 198.61)	-0.27 (24)	0.790
Serum iron	11.40 (7.64)	9.40 (6.70)	-2.56 (-11.20, 5.23)	-1.98 (22)	0.060*
TIBC	41.83 (11.25)	43.89 (12.24)	2.46 (-7.63, 2.71)	0.99 (20)	0.333

[a]Paired *t* test was applied

Table 5. Comparison of mean haematological parameters and iron status between two groups before EPO treatment

Variables	CAPD (n = 20)	Haemodialysis (n = 25)	Mean diff (95% CI)	t-stat[a] (df)	p-value
	Mean (SD)	Mean (SD)			
Haemoglobin	9.73 (1.10)	9.34 (1.56)	0.39 (-0.44, 1.22)	0.94 (43)	0.350
MCV	86.89 (4.67)	91.56 (8.46)	-4.67 (-8.93, -0.41)	-2.21 (43)	0.032
MCHC	32.60 (0.10)	31.72 (1.87)	0.88 (0.03, 1.73)	2.10 (43)	0.042
WBC	7.82 (1.81)	8.06 (2.64)	-0.24 (-1.64, 1.16)	-0.35 (43)	0.731
Platelet count	283.20 (58.91)	226.80 (66.17)	56.40 (18.25, 94.55)	2.98 (43)	0.005*
Ferritin	746.80 (337.24)	615.76 (661.52)	131.04 (-197.28, 459.36)	0.80 (43)	0.425
Serum iron	13.77 (7.64)	11.40 (7.64)	2.37 (-2.25, 6.99)	1.03 (43)	0.307
TIBC	41.60 (11.66)	41.83 (11.25)	-0.23 (-7.15, 6.69)	-0.07 (43)	0.947

[a]Independent *t* test was applied

Statistical analysis

Statistical Program for Social Science Software (SPSS), version 18.0.1, was used for data entry and data analysis. All the data were double checked and cleaned to verify that the entire variables were properly documented and to detect any missing or erroneous values during data entry.

Exploration of data was then conducted to obtain descriptive statistics. Paired t test was used to compare the mean values of the haematological parameters and iron status between pre and post EPO treatment within each CAPD and haemodialysis group of patients. Meanwhile, independent t test was used to compare the mean values of the haematological parameters and iron status between two groups for each of the measurements.

RESULTS

A total of 20 patients in CAPD group were recruited in the study which consisted of 11 males and nine females aged ranging from 54 to 58 years old. On the other hand, a total of 25 patients in haemodialysis group were included which comprised 13 males and 12 females with aged ranging from 44 to 46 years old.

The result showed differences in mean MCV, lymphocyte count, platelet count and TIBC between pre-EPO and one month post-EPO levels in CAPD group of patients **Table I**. There were significant increments of mean MCV, TIBC and lymphocyte count values at one month post-EPO compared to pre-EPO levels. On the other hand, the mean of platelet count decreased at one month post-EPO. The result was consistent for platelet count where there was a significant reduction of mean platelet count between pre-EPO and three months post-EPO in the same group of patients **Table 2**.

For haemodialysis group of patients, there was a significant difference in mean haemoglobin between pre-EPO and one month post-EPO (mean difference = 1.01; 95% CI: -1.65, -0.38; p = 0.030) **Table 3**. The result remained same for three months post-EPO where there was a significant difference for haemoglobin between pre-EPO and three months post-EPO but not for other haematological parameters and iron status **Table 4**.

Before EPO treatment was given, there were significant differences of mean MCV, MCHC and platelet count between CAPD and haemodialysis groups of patients **Table 5**. The results show that the mean MCV was higher in haemodialysis group, while mean MCHC and platelet count were higher in CAPD group. After one month post-EPO, there was a significant difference of mean serum iron between these two groups where the mean value of serum iron was higher in CAPD group of patients **Table 6**. Meanwhile, after three months post-EPO, there were significant differences of mean white blood cells and serum iron between the two groups of patients **Table 7**. The mean white blood cell was higher in haemodialysis group and the mean serum iron was higher in CAPD group.

Table 6. Comparison of mean haematological parameters and iron status between two groups one month after EPO treatment

Variables	CAPD (n = 20)	Haemodialysis (n = 25)	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	10.08 (1.58)	10.35 (1.54)	-0.27 (-1.21, 0.67)	0.58 (43)	0.567
MCV	90.69 (5.65)	91.12 (7.83)	-0.43 (-4.64, 3.78)	-0.21 (43)	0.838
MCHC	32.33 (1.03)	31.49 (2.48)	0.84 (-0.36, 2.04)	1.42 (43)	0.164
WBC	7.02 (5.65)	8.51 (5.40)	-1.49 (-4.82, 1.84)	-0.90 (43)	0.373
Platelet count	252.40 (39.49)	224.16 (64.75)	28.24 (-5.06, 61.54)	1.71 (43)	0.094
Ferritin	651.92 (370.59)	596.37 (619.07)	55.55 (-261.48, 372.58)	0.35 (43)	0.726
Serum iron	13.02 (5.41)	7.97 (5.07)	5.05 (1.89, 8.21)	3.22 (43)	0.002*
TIBC	43.63 (7.53)	39.12 (8.46)	4.51 (-0.37, 9.39)	1.86 (43)	0.069

[a]Independent *t* test was applied

Table 7. Comparison of mean haematological parameters and iron status between two groups three months after EPO treatment

Variables	CAPD (n = 20)	Haemodialysis (n = 25)	Mean diff (95% CI)	t-stat[a] (df)	*p*-value
	Mean (SD)	Mean (SD)			
Haemoglobin	14.92 (18.62)	11.22 (1.45)	3.70 (-3.82, 11.22)	0.99 (43)	0.326
MCV	87.68 (14.04)	90.22 (8.47)	-2.54 (-9.36, 4.28)	-0.75 (43)	0.457
MCHC	31.17 (6.05)	31.87 (1.98)	-0.70 (-3.29, 1.89)	-0.54 (43)	0.589
WBC	7.03 (1.79)	8.57 (2.83)	-1.54 (-3.01, -0.07)	-2.12 (43)	0.040
Platelet count	230.24 (75.62)	225.12 (61.29)	5.12 (-36.02, 46.26)	0.25 (43)	0.803
Ferritin	625.48 (355.30)	592.80 (894.64)	32.68 (-396.19, 461.55)	0.15 (43)	0.879
Serum iron	15.13 (9.70)	9.40 (6.70)	5.73 (0.79, 10.67)	2.34 (43)	0.024*
TIBC	44.57 (9.01)	43.89 (12.24)	0.68 (-5.93, 7.29)	0.21 (43)	0.837

[a]Independent *t* test was applied

DISCUSSION

The results of this study showed that the haemoglobin level in the haemodialysis group of patients was found to be 9.34 (1.56) g/dl pre treatment and this increased to 10.35 (1.54) g/dl after one month and 11.22 (1.45) g/dl after three months on EPO therapy. After three months on intravenous EPO, the haemoglobin level was increased by 1.88 g/dL. On the other hand, the haemoglobin level in CAPD group of patients increased by 5.19 g/dl after three months of subcutaneous EPO treatment. However, these findings were not statistically significant and this could be due to the relatively small sample size.

Both groups of patients managed to achieve a target haemoglobin level of 11 to 12 g/dl. It is interesting to note that the rise in haemoglobin was greater in the CAPD group compared to the haemodialysis group after three months post-EPO. This is in contrast to results of a study conducted in older Medicare enrollees by Synder *JJ,et al*., (2004) whereby patients who received peritoneal dialysis were substantially less likely to have initiated erythropoietin than patients who received haemodialysis. In both groups, the target haemoglobin level was achieved. The Haemoglobin level of the haemodialysis group was greater than that of the CAPD group[22].

It has long been believed that CAPD patients tend to be less anaemic than haemodialysis patients[23,24]. This study reported that the ferritin level reduced after treatment with recombinant human erythropoietin in both CAPD and haemodialysis groups. Similar result by another study showed that CAPD patients treated with rHuEPO was associated with a decrease in ferritin[26].

The present study also revealed that subcutaneous rHuEPO was more effective in treating anaemia in CAPD patients compared to intravenous route of administration in haemodialysis patients. This was reported from the overall results of the parameters evaluated where those of the CAPD group showed higher changes compared to the haemodialysis group. An acceptable target haemoglobin concentration can be achieved with considerably lower dose erythropoietin of subcutaneous rHuEPO than those normally recommended.

A study by Besarab *et al*., (2002) in the United States, reported that erythropoietin is usually given intravenously to haemodialysis patients and subcutaneously to peritoneal dialysis patients. The subcutaneous route is believed to be more efficacious in terms of haemoglobin level achieved[21]. There are also other studies that suggested anaemia is less common and more sensitive to erythropoietin in CAPD patients than in haemodialysis patients, possibly because blood loss is less marked and residual renal function may be better preserved in patients who received peritoneal dialysis. Besid blood is usually drawn before a dialysis session; as a result, haemoglobin is likely to be partly diluted[25,26].

A decrease in erythropoietin response similar to our findings was reported in another study[27]. The study was restricted to older patients in the first year of dialysis therapy. It is unlikely those haemodialysis patients, on average, have more co-morbid conditions at the inception of dialysis therapy, which may well decrease erythropoietin responsiveness.

On evaluating the iron status of patients, the present study showed a significant increase in the mean TIBC level of patients undergoing CAPD and after one month treated with rHuEPO. TIBC also increased by 2 µmol/L in the haemodialysis group after three months of treatment but it was not statistically significant. Mean MCV was increased in the CAPD group but reduced in the haemodialysis group. Serum iron showed a mild increase of 1.36 µmol/L in the CAPD group, while it decreased by 2.56 µmol/L in the haemodialysis group. Ferritin levels in both dialysis groups reduced post-treatment compared to pre-treatment levels, though this was not statistically significant. Iron deficiency is one of the most common complications in patients suffering from CRF and undergoing dialysis.

The anaemia leads to severe impairment of quality of life and is associated with a decreased haemoglobin level and MCV concentration. The administration of erythropoietin leads to stimulation of the bone marrow production of red blood cells, which results in an increase in haemoglobin level, MCV, serum iron, serum ferritin and TIBC and improves the quality of life of patients. EPO therapy will reduce the exposure of patients to red blood cells transfusions to avoid the results of adverse effects of blood transfusion. The most important goals of erythropoietin treatment are avoidance or elimination of blood transfusion and improved quality of life.

Low or decreased serum iron status may be a result of increased level of circulating cytokine capable of inducing macrophages of reticuloendothelial system that hold on iron which may lead to a decrease in the endogenous EPO production or decreased responsiveness of erythroid precursor cells to endogenous or exogenous EPO. Various reasons could have caused the reduced platelet counts in both groups of patients in the present study. Some of these reasons may include platelet dysfunction which is common in CRF. Others may include uremia, hereditary thrombocytopenia and drugs.

There were few limitations of the present study. Some data were missing from the clinical records of patients. This suggests proper documentation is very important. The short study period only allowed evaluation of rHuEPO treatment up to three months. However, as patients are treated on a long term basis with rHuEPO, it would be useful to track their haemoglobin and iron status over a longer period of time. Other confounding factors that may affect haemoglobin and iron status included patients' diet, compliance to dietary supplement pills from hospital, other underlying chronic diseases such as hypertension, diabetes, blood loss during menstruation in women and blood loss due to other conditions.

CONCLUSION

CRF patients undergoing dialysis respond to EPO treatment and Subcutaneous EPO administration and intravenous EPO. The haemodialysis group was healthier than the CAPD group. However, other confounding factors need to be considered.

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