The Prevalence of Iron Deficiency Anemia in Chronic Renal Failure at Maharat Nakhon Ratchasima Hospital

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Abstract The purpose of this descriptive cross-sectional pilot study was to determine the prevalence of iron deficiency anemia in non-dialysed adult patients with chronic renal failure presenting to Maharat Nakhon Ratchasima Hospital from November, 1993 to January, 1994. Twenty-eight patients; 12 male (42.9%) and 16 female (57.1%), with chronic renal failure who had serum creatinine 4mg/dl were included in the study. History taking and physical examinations were done in all patients on arrival at the hospital. Laboratory investigations including routine urine analysis, stool examination, CBC, Hb typing, BUN, serum creatinine and LFT were performed in all cases. Ultrasonogram of the kidneys were performed in 25 cases. Blood samples were also taken for special nutritional laboratory investigations including serum iron, vitamin B12, serum folate, red cell folate and TIBC. Bone marrow aspiration was performed in all patients for determination of iron storage, cellularity and myeloid erythroid ratio. All patients were found to be anemic (Hb<12mg/dl for female and <13mg/dl for male). All patients except four (14.3%) had stainable marrow iron. Two (7.1% of all cases) of the four patients with no 'stainable iron were associated with iron deficiency anemia as shown by low level of hemoglobin, MCV, serum iron, and high TIBC and no hemoglobinopathy. These results showed that the prevalence of anemia in Thai patients with chronic renal failure are 100% but only 7.14% of the patients had iron deficiency anemia. The incidence of hemoglobinopathies in Thai patients with CRF are also high (Hb E 33.3%, thalassemia trait 40.7%). There was a significant negative correlation between the hematocrit or the hemoglobin concentrations and serum creatinine levels.

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บทคัดย่อ รายงานนี้เป็นการศึกษาเชิงพรรณนาเพื่อหาอุบัติการณ์ของภาวะโลหิตจางจากการขาดธาตุเหล็กในผู้ป่วยไตวายเรื้อรังที่ยังไม่ได้รับการบำบัดทดแทนไต ที่โรงพยาบาลมหาราชนครราชสีมา ตั้งแต่เดือนพฤศจิกายน 2536 – มกราคม 2537 ได้ศึกษาผู้ป่วยจำนวน 28 ราย เพศชาย 12 ราย (ร้อยละ 42.9) เพศหญิง 16 ราย (ร้อยละ 52.1) ทั้งหมดมีระดับครีตินินในเลือดมากกว่า 4 มก/ดล ผู้ป่วยทั้งหมดได้รับการซักประวัติ ตรวจร่างกาย ตรวจทางห้องปฏิบัติการได้แก่ CBC, BUN, Cr, electrolytes, urine analysis, stool examination และส่งการตรวจพิเศษ ได้แก่ hemoglobin typing, serum iron, TIBC, serum folate, red blood cell folate, serum vitamin B12 และ bone marrow aspiration เพื่อดูปริมาณเหล็ก พบว่าผู้ป่วยทั้งหมดมีภาวะโลหิตจาง ตาม WHO criteria 4 รายไม่พบว่ามี iron stained ใน bone marrow ผู้ป่วย 2 ใน 4 รายนี้พบว่ามี ระดับ serum iron, MCV ต่ำ มี TIBC สูงและไม่มี abnormal hemoglobin ซึ่งเข้าได้กับภาวะโลหิตจางจากการขาดธาตุเหล็ก ผลการศึกษานี้พบว่าอุบัติการณ์ของภาวะโลหิตจางจากการขาดธาตุเหล็กในผู้ป่วยไตวายเรื้อรังเท่ากับร้อยละ 7.14 และมีอุบัติการณ์ของ abnormal hemoglobin สูงถึงร้อยละ 33 (Hb E ร้อยละ 33.3, thalassemia trait ร้อยละ 40.7) จากการศึกษายังพบว่ามีความสัมพันธ์แปรผกผันกันอย่างมีนัยสำคัญทางสถิติระหว่างค่า hemoglobin, hematocrit และ serum creatinine

Chronic renal failure is almost invariably accompanied by symptomatic anemia [1-5] as one of the commonest early clinical manifestations. [4,6] Anemia in patients with renal disease was first reported by Richard Bright in 1836 and after that, numerous researchers have tried to characterize and clarify the underlying anemia. [1] The severity of anemia seems to be roughly proportional to the severity of azotemia [1,2,6-8] but it is not astonishing that an absolute linear correlation does not exit. A fall in the hematocrit may be caused by any one of a number of changes in the rate of red cell production and red cell destruction, and an increase in serum creatinine may be caused by a variety of infectious, neoplastic, allergic, metabolic, or hydrodynamic injuries to the renal parenchyma. [1] However, the hematocrit is almost always below 30 percent at creatinine clearances below 20 ml/min. [8] Additionally, the etiology of anemia in chronic renal failure is multi-factorial. [3,7] Both failure of renal endocrine function leading to impaired erythropoietin production and failure of renal excretory function leading to blood loss, marrow depression, and hemolysis cause anemia in CRF. [1] Since iron deficiency may be an important component of this anemia [3,9] and the management of anemia is one of the persistent medical problems in the management of chronic renal failure [4,9] and no such study has be so far done in Thailand. Therefore, this (descriptive) cross sectional pilot study was carried out to determine the prevalence of iron deficiency anemia in non-dialysed adult patients with chronic renal failure presenting to Maharat Nakhon Ratchasima Hospital from November 15, 1993 to January 7, 1994. Abnormal hemoglobin is common cause of anemia in Thailand. The incidence of hemoglobinopathies is high. The prevalence of hemoglobin E and thalassemia varied in different regions of Thailand. In Nakhon Ratchasima, the incidence of Hb E and thalassemia trait was 11% and 1.7% respectively. [10,11]

Methods This study included all patients aged ≥ 1 8 years old who were diagnosed as CRF by serum creatinine ≥ 4 mg/dl and no previous history of

hemodialysis and peritoneal dialysis intervention. All cases had their blood checked for BUN, creatinine and CBC from OPD clinic before being admitted to the medicine wards. After admission, all of them had their demographic information, their history of present and previous illness taken. Their physical examination was performed and recorded in the case record form. Further blood investigations for CBC, serum creatinine, BUN, LFT, electrolytes and Hb typing were done before blood or any blood component transfusion, iron supplementation, folic acid and vitamin therapy or dialysis would be done. Informed consent was filled up in every case before bone marrow aspiration would be performed. In addition, stool and urine examination were performed. Kidney ultrasonography was done in 23 cases to support the diagnosis. [12]

Data were entered into a computer file using EPI Info program. Correlations between hemoglobin, hematocrit and bone marrow iron and creatinine was analyzed by using Pearson's Product-Monent correlation coefficient test at alpha 0.5.

Results Totally 28 patients with chronic renal failure were included in this study. Complete hematologic study of anemia was done in only 26 patients due to inadequate bone marrow aspiration slide in one and a missing blood sample for iron study, TIBC, serum and red cell folate in the other.

Out of 28 patients, 16 were male and 12 were female with the mean age of 55.96 years old (range from 21 to 78, median 59). Most patients were farmer and jobless (n=12 and n=11, respectively). The underlying causes of chronic renal failure were hypertension in 8 patients, diabetes mellitus in 3 patients and both hypertension and diabetes mellitus in another 3 patients. The remaining patients, the cause of chronic renal failure could not be determined (table 1). Ultrasonogram of kidneys was performed in only 23 patients, bilateral small kidneys (<9 cm) were found in 20 (87%) patients, 1 (4.3%) patient had evidence of hydronephrosis due to ureteric stone, the other 2 patients had normal size kidney with abnormal parenchyma suggestive of chronic renal disease.

The mean creatinine and BUN values were 11.74 mg/dl and 114.59 mg/dl (range from 4.5 mg/dl to 27.62 mg/dl and 30.25 mg/dl to 207.93 mg/dl) respectively. Anemia was found in virtually all patients (WHO criteria, Hb<13gm/dl for men and Hb<12gm/dl for women). The anemia was characteristically microcytic hypochromic in 15 (53.6%) patients, normocytic normochromic in 8 (28.6%) patients and microcytic normochromic in 4 (14.3%) patients (table 2). The value of MCV, MCH, MCHC, BUN, serum creatinine and LFT was shown in table 3 . The value of serum iron, UIBC, TIBC, serum folate, red blood cell folate, serum vitamin B12 and bone marrow iron was shown in table 4 .

Iron study showed that serum iron was lower than normal in 5 (18.5%) patients, normal in 20 (74%) patients and high in 2 (7.4%) patients. TIBC was found higher than normal in 7 (29.9%) patients, normal in 15 (55.6%) and lower than normal in 5 (18.5%) (table 5).

Only 1 (3.7%) patient was found to be having low serum vitamin B12, 4 (14.8%) were found within normal level and 22 (81.5%) were found higher level. Low level of serum folate was seen in 9 (33.3%) patients and 8 (29.6%) were found high level of serum folate. Red blood cell

folate was found lower in 10 (37%), higher in 10 (37%) patients and the rest 7 (25.9%) were found normal (table 6).

Bone marrow aspiration study showed absence of the bone marrow iron storage in 4 (14.3%) patients. The remaining 23 (85.7%) patients presented the existence of bone marrow iron storage. Of which 5 (18.5%), 8 (29.6%) and 6 (22.2%) were found to be 1^+, 2^+, 3^+ and 4^+ respectively.

Hemoglobin typing was performed in 27 patients, hemoglobinopathies were found in 20 (74.1%) patients. Of these, thalassemia trait was seen in 11 (40.7%) patients, Hb E trait was found in 8 (29.6%) patients and 1 (3.7%) showed Hb E homozygote (table 7).

There were significant negative correlations between hemoglobin concentration, hematocrit and serum creatinine. The high creatinine value the lower hemoglobin and hematocrit were obtained (table 8)

Discusion WHO expert committee defined anemia as a reduction of the hemoglobin concentration, the hematocrit or the number of red blood cells, to a level below that which is normal for a given individual. In this study, the hemoglobin concentration less than 12 gm/dl for women and 13 gm/dl for men are also considered as a nemic as defined by WHO. In this study, all the male and female patients with chronic renal failure were anemic despite hematinic supplementation in 57.1% of patients. The prevalence of anemia is 100% and of these 89.3% are severe anemia (Hb<10gm/dl). This corresponded with other studies where the prevalence of anemia in chronic renal failure was almost 100%. [1-5] However, the prevalence of iron deficiency anemia (7.1%) was probably much lower in this study than that really existed because 12 patients had been on oral iron supplementation for sometime and one previously had blood transfusion.

Anemia in this study population may not be due mainly to iron deficiency. The causes of anemia in chronic renal failure are multifactorial. [3,7] Either failure of endocrine function resulting in a decreased erythropoietin production or failure of excretory function resulting in blood loss, marrow depression, and hemolysis cause anemia in chronic renal failure. [1] Additionally, reduced dietary intake of iron and other hematinics due to anorexia[6] and dietary restriction, and impaired intestinal absorption [6] also lead to anemia. The same could be said for this study. However, the high prevalence of hemoglobinopathy in the study population and under the stressful condition of an increased serum creatinine can also change the life span of red cells significantly. This may also be one of the possible causes of anemia in this study population.

The serum iron, the serum folate, the red cell folate and the serum vitamin B12 concentration of some patients were exceptionally high because they have been supplemented iron and multivitamin. The bone marrow of 9 patients showed somewhat normal stainable iron, the marrow of 14 of the remainder had increased stainable iron and only 4 patients showed no stainable iron in their marrow. This finding is typical of the anemia of chronic disorders in which the stainable marrow iron may be normal or increased. Moreover, it is difficult to interpret in 4 cases of no stainable iron. The absence of iron on an aspirates specimen is not unequivocal evidence of absent stores and iron was detectable in the biopsy specimen in more than 33% of marrow aspirates considered to have absent

Table 1 Baseline information according to WHO criteria (n=28)

	Female Hb<12gm/dl no. of patients(%) (n = 18)	Male Hb<13gm/dl no. of patients(%) (n = 12)	Total
Age (yr):			
20–29	2 (12.5)	0	2
30–39	2 (12.5)	1 (8.33)	3
40–49	2 (12.5)	0	2
50–59	3 (18.7)	1 (8.33)	4
60–69	6 (37.5)	4 (33.3	10
70–79	1 (6.25)	6 (50)	7
Occupation :			
No job	7 (43.7)	4 (33.3)	11
Farmer	5 (31.2)	7 (58.3)	12
Employee	3 (18.7)	0	3
Goverment official	1 (6.25)	0	1
Other	0	1 (8.33)	1
Associated disease :			
Diabetes mellitus (DM)	3 (25)	2 (16.6)	5
Hypertension (HT)	4 (50)	4 (66.6)	8
DM+HT	2 (25)	1 (16.6)	3

Table 2 Hemoglobinopathies in 27 patients

	Microcytic hypochromic* no.(%)	Normocytic normochromic† no.(%)	Microcytic normochromic‡ no.(%)
Normal	3 (20)	2 (25)	2 (50)
Hb E trait	8 (53.3)	0	0
Hb E homozygote	1 (6.7)	0	0
Thalassemia trait	3 (20)	6 (75)	2 (50)
Total	15 (100)	8 (100)	4 (100) §

* MCV < 80 fl+MCH < 27pg

† MCV = 80–100 fl+MCH < 27pg

‡ MCV = 80–100 fl + MCH = 27–32 pg.

§ Excluding 1 patient without Hb typing

Table 3 Routine investigations (n=28)

	Median	Range	Mean (SD)	Normal
BUN (mg/dl)	114.51	30.25–207.94	114.59 (41.10)	10.2
Cr (mg/dl)	9.805	4.46–27.62	11.47 (5.88)	1–2
Hb (g/dl)	6.1	3.60–12.0	6.68 (2.30)	12.0–13.0
Hct (%)	18.3	10.20–35	18.97 (6.62)	33%
MCH (pg)	26.15	14.30–32.68	25.74 (5.46)	27–33
MCV (fl)	73.8	46.40–93.70	74.12(10.49)	82–96
MCHC (g/l)	35.4	30.80–38.10	35.39 (1.5)	31.7 34.1
Retic. Count (%)	0.5	0.2–5.5	1.10 (1.41)	0.2–2
AST (IU)	13.67	3.47–203.94	24.28 (28.82)	< 40
ALT (IU)	24.28	13.77–138.07	36.92 (32.94)	< 40
Alk phosp (IU)	48.13	5.02–131.74	53.39 (29.57)	9.0–35
T bili (mg/dl)	0.4	0.12–17.85	1.12 (3.35)	9.0–35.0
D bili (mg/dl)	0.17	0.04–5.85	0.41 (1.09)	0 – 0.2
T prot (gm/dl)	6.44	4.45–9.16	6.34 (1.03)	6.6 – 8.3
Albumin (gm/dl)	3.95	1.81–6.12	3.84 (0.90)	3.8 – 5.1

Table 4 Specific investigations (n=27)

	Median	Range	Mean (SD)	Normal
Serum Iron (g/dl)	118.54	65.0–174.0	119.0 (30)	123±38
UIBC (g/ml)	208.5	70.0–465	232.39(107)	210±70
TIBC (g/ml)	331.0	187.0–583	350.89(99.52)	328±59
Serum folate (ng/ml)	8.55	0.5–84	14.39(17.67)	9.8±5
RBC folate (ng/ml)	670.5	43–4683	1087.2(1032.83)	727±247
Serum vit B12 (pg/ml)	912.5	288–13580	2221.64(3210.55)	629±160
BM iron	2.30	0–4	2.5(1.38)	2

Table 5 Results of serum iron (SI), total iron binding capacity (TIBC) and transferrin iron saturation (TIS) (n=27)

	SI no.(%)	TIBC no.(%)	TIS no.(%)
Low	5 (18.5)	5 (18.5)	2 (7.4)
Normal	20 (74)	15 (55.6)	19 (70.4)
High	2 (7.4)	7 (29.9)	6 (22.2)
Total	27 (100)	27 (100)	27 (100)

SI = 123±38 g/100ml TIBC = 328±59 g/100ml

TIS = 35±15%

Table 6 Results of serum vitamin B12 , seum folate and red blood cell folate (n =27)

	Serum vitamin B12 no.(%)	Serum folate no.(%)	Red blood cell folate no.(%)
Low	1 (3.7%)	9 (33.3)	10 (37)
Normal	4 (14.8)	10 (37)	7 (25.9)
High	22 (81.5)	8 (29.6)	10 (37)
Total	27 (81.5)	27 (100)	27 (100)

Serum vitamin B12 = 629±160 pg/ml Serum folate = 9.8±5 ng/ml

Red blood cell folate = 727±247 ng/ml

Table 7 Hemoglobin typing of 27 patients

	No. of patients	Percentage
β trait	11	40.7
E trait	8	29.6
E homozygote	1	3.7
Normal Hb	7	25.9
Total	27	100

Table 8 Correlations between creatinine and other variables

	r value	95% CI	P value
Hb	−0.55	−0.77 to −0.22	<0.05
Hct	−0.54	−0.76 to −0.20	<0.05
Serum folate	−014	−049 to 0.26	>0.05
Serum iron	0.02	−0.36 to 0.40	>0.05
Serum vitamin B12	0.11	0.29 to 0.47	>0.05
RBC folate	0.13	0.26 to 0.49	>0.05
TIBC	0.13	0.26 to 0.49	>0.05

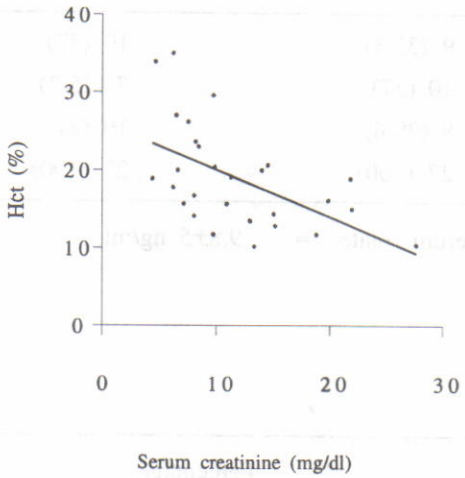

Figure 1 Correlation between serum creatinine and hematocrit

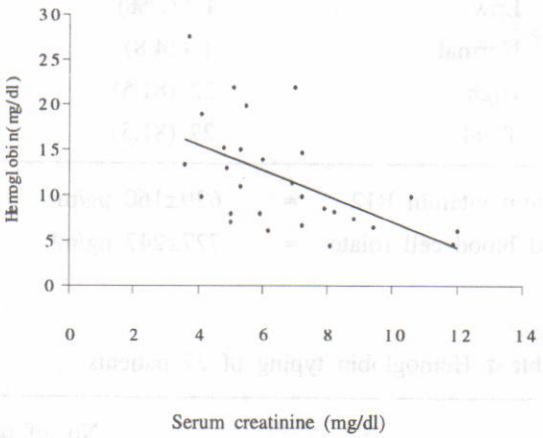

Figure 2 Correlation between serum creatinine and hemoglobin

iron on an aspirated sample. Therefore, the lack of stainable marrow iron on an aspirates must be confirmed by marrow biopsy or serum ferritin. [13] Of 27 marrow aspirates, only 2 of the 4 cases with no stainable marrow iron were consistent with having iron deficiency anemia (microcytic hypochromic anemia with serum iron and TIS lower than nornal, high TIBC and no associated hemoglobinopathy) and the remainder 2 with iron deficient erythropoiesis (normocytic normochromic anemia with serum iron and TIS higher than normal).

The observation has also supported the report of Callen and Limazari. [7] The marrow cellularity of our patients were almost normal but the marrow of six patients showed some what hypoplastic.

The red cells in chronic renal failure are usually normocytic and normochromic, [2] but in our study we found only 8 patients with normocytic normochromic anemia. Of the rest, microcytic hypochromic anemia was detected in 16 patients and microcytic normochromic anemia in 4 patients. This dissimilarity is due most probably to the high prevalence of hemoglobinopathy, especially Hb E trait and homozygous, in the northeastern region of Thailand, 9 of these groups of patients in our study were associated with mainly Hb E and 2 patients in these groups had iron deficiency anemia.

Eschbach and Adamson have commented that the anemia in chronic renal failure is associated with a normal or slightly decreased number of reticulocytes. [14] We also observed anemia with normal number reticulocytes, but four cases of anemia were associated with slightly increased number of reticulocytes due to response of bone marrow to destruction of RBC and no case with decreased number of reticulocytes was seen. On the other hand, our finding contrasted with the report of Shaw and Scholes in which reticulocytes count was remarkably decreased in uremic patient. [15]

In this study, I also found a significant negative correlation between the hemoglobin concentration and the serum creatinine level. There was also a significant negative correlation between the hematocrit and the serum creatinine level among the 16 patients who had not taken oral iron medication. These findings are compatible with the observation in the studies by Radthke et al [8] and Mc Gonigle et al. [16]

Conclusion This descriptive cross-sectional pilot study was carried out to determine the prevalence of iron deficiency anemia in chronic renal failure at Maharat Nakhon Ratchasima Hospital from November 15, 1993 to January 7, 1994. The prevalence of anemia and iron deficiency anemia were 100% and 7.1% (CI=6.9-7.3%) respectively. The prevalence of hemoglobinopathy was high among the patients with chronic renal failure (Hb E = 33.3%, thalassemia trait = 40.7%). There was a significant negative correlation between the serum creatinine levels and the hematocrit or the hemoglobin concentrations. Eighty-seven percent of the patients had bilateral small and contracted kidneys. Other findings were more or less similar to those of other studies. I recommended to use larger sample, excluded those who has been taking iron supplement and who has hemoglobinopathy if similar study is going to carry out in the future.

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