Prevalence of Hemoglobin Cycling and Its Clinical Impact on Outcomes in Thai End-Stage Renal Disease Patients Treated with Hemodialysis and Erythropoiesis-Stimulating Agent

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Background: *Erythropoiesis-stimulating agent (ESA) treatment is the optimal therapy for anemia in end-stage renal disease (ESRD) patients receiving hemodialysis. During treatment with ESA, the level of hemoglobin usually fluctuates widely; this phenomenon is known as "hemoglobin cycling" and may be associated with higher rates of mortality.*

Objective: *To estimate the prevalence of hemoglobin cycling in Thai ESRD patients treated with chronic maintenance hemodialysis and ESA, to assess its clinical impact on patient outcomes, and to identify the associated risk factors for hemoglobin cycling occurrence.*

Material and Method: *An analytic retrospective study was conducted of 150 patients on chronic hemodialysis who were treated with ESA at Rajavithi Hospital and the Kidney Foundation of Thailand at Priest's Hospital between January 2008 and December 2010. Hemoglobin cycling was defined as hemoglobin variability over a period of at least 8 weeks and amplitude of more than 1.5 g/dl.*

Results: *Hemoglobin cycling was experienced by 90.7% of patients. The mean amplitude was 2.4±0.7 g/dl and mean duration of hemoglobin cycling was 8.5±5.0 weeks. Most patients (34.7%) experienced two episodes. The mean level of hemoglobin in patients with hemoglobin cycling (gr. I) and those without it (gr. II) were 10.1±0.9 g/dl and 10.2±0.7 g/dl respectively (p = 0.60). The mortality and hospitalization rates in gr. I and II were not significantly different (OR = 2.52; 95% CI: 0.31-20.27, p = 0.70 and OR = 1.65; 95% CI: 0.43-6.18, p = 0.56 respectively), and the numbers of ESA dose adjustments in gr. I and gr. II were also not significantly different (7.2±2.4 vs. 8.2±1.7 dose change/patient/year, p = 0.14). The serum levels of blood urea nitrogen, creatinine, intact parathyroid hormone, ferritin, % transferrin saturation, weekly Kt/V_{urea} and co-morbidity (diabetes mellitus, congestive heart failure, cerebrovascular disease and hypertension) were not significantly different in the two groups of patients.*

Conclusion: *Hemoglobin cycling was commonly found in Thai ESRD patients treated with hemodialysis and ESA. The influence of hemoglobin cycling on mortality and hospitalization rates could not be significantly demonstrated in the present study; however, both mortality and hospitalization rates showed an upward trend in patients with hemoglobin cycling.*

Keywords: *Anemia, Erythropoiesis-stimulating agent, Hemoglobin cycling, Hemodialysis*

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Anemia of chronic kidney disease (CKD), which arises from inadequate production of erythropoietin (EPO) by the failing kidney in response to declining hemoglobin concentration, is a well-recognized complication in end-stage renal stage (ESRD) patients receiving chronic maintenance hemodialysis. It has been confirmed as a contributing factor in several symptoms associated with CKD, including fatigue, lethargy, depression, anorexia, reduced exercise tolerance, dyspnea, decreased cognition and mental acuity, as well as cardiovascular consequences such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction[1]. It is also associated with an augmented risk of hospitalization, extended length of hospital stay, and

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with an increased risk of morbidity and mortality associated with cardiovascular disease[2,3]. Since becoming clinically available, erythropoiesis-stimulating agent (ESA) has become the primary therapeutic option for the management of anemia in CKD and hemodialysis patients. Observational evidence has shown that correction of low hemoglobin levels is related to improved survival in dialysis patients[4]; however, it has also been established that there is little benefit, and even a potential risk of increased morbidity and mortality, associated with targeting and maintaining hemoglobin levels >13 g/dl in predialysis CKD patients. As a result, the NKF-K/DOQI and European Renal Best Practice (ERBP) guidelines have recommended that the selected hemoglobin target should normally be in the range of 11-12 g/dl in all patients with CKD[5,6]. Nevertheless, maintaining hemoglobin levels within a narrow target range in dialysis patients is not an easy task due to the high degree of hemoglobin variability observed in these patients[7]. For example, a survey by Lacson et al[8] showed that 62% of hemodialysis patients receiving ESA had hemoglobin levels above or below the target range of 11-12 g/dl, and only one-third (38%) of patients had hemoglobin within the target range. Recombinant EPO therapy is quite different from the biologic processes of erythropoiesis; for example, in its short duration, its intermittent use, and its attendant non-physiologic explosions of EPO availability in the plasma after an injection. It may not be surprising, therefore, that during treatment with ESA in hemodialysis patients, the levels of hemoglobin tend to swing up and down in a cyclic pattern known as "hemoglobin cycling[7]" or "hemoglobin variability[9]". Recently, it has been reported that hemoglobin cycling may have an unfavorable impact on patient outcomes and may be independently associated with higher mortality[9,10]. The phenomenon of hemoglobin cycling has yet not been widely studied in Thailand; therefore, the purpose of the present study was to evaluate its prevalence in Thai ESRD patients receiving maintenance hemodialysis treated with ESA, to assess its impact on the hospitalization and mortality rates of these patients, and to identify the associated risk factors for hemoglobin cycling events.

Material and Method

Patients

An analytic retrospective study was conducted of ESRD patients receiving chronic maintenance hemodialysis who were treated with ESA at Rajavithi Hospital and the Kidney Foundation of Thailand at Priest's Hospital between January 2008 and December 2010. Patients were recruited into the study if they: (1) were aged ≥18 years old; (2) had received hemodialysis for at least 6 months; and (3) were treated with short-acting ESA on a regular basis. Patients were excluded when any of the following criteria was met: (1) history of red blood cell transfusion; (2) history of gastrointestinal bleeding or other major bleeding within 6 months; (3) hemolytic anemia; or (4) patients with malignant disorders or HIV infection.

Written informed consent was obtained from all participants after they had received verbal and written descriptions of the study protocol, which was reviewed and approved by the Ethics Committee of Rajavithi Hospital.

Methods

All patients who were receiving chronic maintenance hemodialysis at either dialysis center were screened for eligibility from their medical records. Their demographic characteristics, which included age, gender, co-morbid diseases, dialysis vintage, and ESA dosage, were reviewed. The prescribed ESAs were short-acting erythropoietin of various brands, and the dosages of ESA were adjusted by each nephrologist in accordance with the guidelines[5,6]. Laboratory data were recorded including: weekly hemoglobin and hematocrit; monthly serum levels of calcium, phosphate, and albumin; serum ferritin, and % transferrin saturation (TSAT) every 6 months; intact parathyroid hormone (iPTH) every 6-12 months; and also the predialysis serum levels of blood urea nitrogen (BUN) and creatinine, including the adequacy of dialysis as measured by weekly Kt/V_{urea} monthly. All the blood samples were collected before the dialysis sessions. Clinical data including number of ESA dose adjustments, number of previous incidences of hospitalization and mortality were recorded. Hemoglobin levels were calculated from the hematocrit using a standard published equation (Hemoglobin [g/dl] = Hematocrit [%]/3)[11]. The ESA dose adjustment for the target hemoglobin depended on the K/DOQI 2006 guideline[12], which was used during the treatment period in the present study.

Definition of hemoglobin cycling

Hemoglobin cycling was defined as non-physiologic oscillation or periodic fluctuations in hemoglobin levels over or under the target range over time in an individual patient. The oscillation was

characterized as >1.5 g/dl from an equilibrium point with reversion back to the same point over a period of at least 8 weeks[7,13]. Half of one hemoglobin cycle was defined as a hemoglobin excursion. The duration of a hemoglobin excursion was defined as the number of weeks from the high and low hemoglobin measures in the excursion. Only excursions of four or more weeks' duration were used for analysis. The amplitude of a hemoglobin excursion was the difference between hemoglobin levels at the start and end of the excursion. Only hemoglobin excursions with amplitude >1.5 g/dl were included in the analysis.

The hemoglobin target range in the present study was 11.0-12.0 g/dl as recommended by the KDOQI guidelines, which were used during the evaluation period[5,6,12]. As a result, the average hemoglobin levels were categorized as low (LOW, <11 g/dl), target (TARGET, 11-12 g/dl), and high (HIGH, >12 g/dl). The pattern of hemoglobin cycling or variability was classified by the 6-group classification system described by Ebben et al[14], based on the lowest and highest categories seen during the evaluation period, as follows: (1) constantly low (LOW, all 3-year with low hemoglobin levels); (2) consistently within the target range (TARGET, all 3-year with target-range hemoglobin levels); (3) consistently high (HIGH, all 3-year with high hemoglobin levels); (4) low-amplitude fluctuation and low hemoglobin levels (LAL; all 3-year with low and target-range hemoglobin levels); (5) low-amplitude fluctuation and high hemoglobin levels (LAH; all 3-year with high and target-range hemoglobin levels); and (6) high-amplitude fluctuation (HA; low, target-range, and high hemoglobin levels) within the 3-year period.

Statistical analysis

Sample size estimation based on proportion[15] was used to determine the sample size in the present study with type I error probability of 0.05. The proportion as reported by Fishbane et al[7] was used as the reference value.

Continuous variables were expressed as mean values $\pm$ standard deviation. Comparisons of groups were analyzed by unpaired t-test or Mann-Whitney U test as appropriate. Chi-squared test or Fisher's exact test were used to test the differences in qualitative variables between groups. A *p*-value of less than or equal to 0.05 was considered to be statistically significant. Data were collected on Microsoft Excel 2010 spreadsheet software and imported into SPSS for Windows version 17 for all statistical analyses.

Results

Patient characteristics

Using 3-year retrospective analysis, a total of 150 chronic hemodialysis patients were identified from the database of patients at Rajavithi Hospital and the Kidney Foundation of Thailand at Priest's Hospital as having met the inclusion criteria and were recruited into the study. Over 50% of these hemodialysis patients were supported by the Social Security fund and the National Health Security Office fund.

The range of mean hemoglobin and hematocrit values of the total patients were 7.9 to 12.5 g/dl and 23.4 to 38.6%, respectively. As shown in Fig. 1, only 11.3% of patients had their mean hemoglobin values in the target range of 11-12 g/dl. Most patients (87.3%) had hemoglobin values of less than 11 g/dl, and only a few patients (1.3%) had their hemoglobin values higher than 12 g/dl.

136 (90.7%) patients showed evidence of hemoglobin cycling according to the definition by Fishbane et al[7] while the remaining 14 (9.3%) patients did not. There were no significant differences in the basic demographic characteristics and clinical data in the two groups of patients (Table 1).

The patients who experienced hemoglobin cycling had a mean number of hemoglobin cycling of 2.1 ± 1.0 per patient over the 3-year period (0.7 ± 0.4 per patient/year). The mean amplitude per hemoglobin excursion was 2.4 ± 0.7 g/dl, and the mean duration of hemoglobin cycling was 8.5 ± 5.0 weeks. The mean levels of hemoglobin, hematocrit, ESA dosage, number of ESA

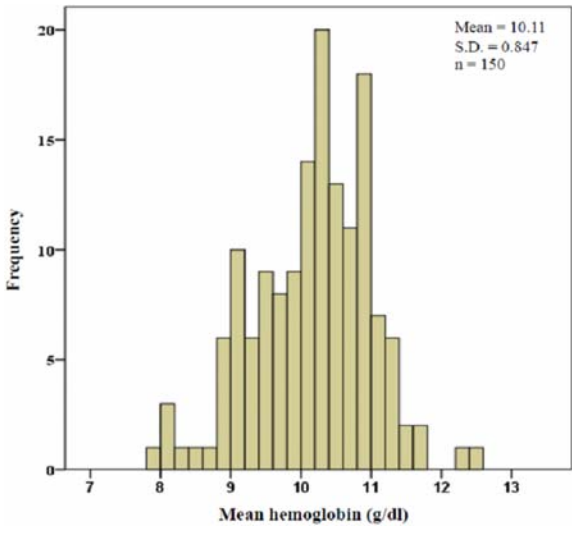

Fig. 1 Distribution of the mean hemoglobin levels in 150 hemodialysis patients.

dose changes, ferritin, % TSAT, iPTH, and other biochemical levels including dialysis adequacy (weekly Kt/V_{urea}) between patients with and without hemoglobin cycling were not significantly different (Table 2).

With regard to the number of hemoglobin cycling episodes, it was found that 9.3% of patients had never experienced hemoglobin cycling during the 3-year period. On the other hand, the percentages of patients who experienced 1 to 5 episodes of hemoglobin cycling were 29.3%, 34.7%, 19.3%, 6.0%, and 1.4%, respectively.

Regarding the fluctuating pattern in hemoglobin levels over time described by Ebben et al[14], in the present study, the percentage of patients stratified in the LAL, HA, and LOW groups were 58%, 28.7% and 13.3%, respectively. No patients had hemoglobin levels in the patterns of TARGET, HIGH, LAH.

Fig. 2 shows a comparison of the mortality and hospitalization rates of patients with and without hemoglobin cycling. The mortality rate in patients with hemoglobin cycling (15.3%) was higher than patients without it (7.1%) but without statistical significance (OR = 2.51, 95% CI: 0.31-20.17, $p = 0.70$). The hospitalization rates in patients with hemoglobin cycling (30.0%) were also higher than patients without it (21.4%) but also without statistical significance (OR = 1.64, 95% CI: 0.43-6.18, $p = 0.56$).

When stratifying the patterns of hemoglobin

Table 1. Demographic characteristics of patients with and without hemoglobin cycling (mean ± SD)

	Total patients	Patients with hemoglobin cycling	Patients without hemoglobin cycling	*p*-values
Number of patients (%)	150 (100)	136 (90.7)	14 (9.3)	
Age (years)	47.3	47.6±11.4	45.2±11.2	0.46
Gender, male (%)	72 (48.0)	65 (47.8)	7 (50.0)	0.86
Hemoglobin (g/dl)	10.1±0.9	10.1±0.9	10.2±0.7	0.60
Hematocrit (vol. %)	30.4±2.6	30.3±2.7	30.7±2.1	0.64
ESA dose (U/week)	5,278±1,936	5,305±1,977	5,011±1,514	0.59
Number of ESA dose change in 3-year period	22.0±7.1	21.7±7.3	24.6±5.0	0.14
Number of ESA dose change/patient/year	7.3±2.4	7.2±2.4	8.2±1.7	0.14
Co-morbidity (%)				
Diabetes mellitus	3.3	2.9	7.1	0.39
Hypertension	60.7	59.6	71.4	0.39
Congestive heart failure	6.0	6.6	0	1.00
Cerebrovascular disease	2.7	2.9	0	1.00
Others	4.7	4.4	7.1	0.50

Table 2. Laboratory data of patients with and without hemoglobin cycling (mean ± SD)

	Patients with hemoglobin cycling	Patients without hemoglobin cycling	*p*-values
BUN (mg/dl)	63.8±12.7	63.9±10.6	0.99
Creatinine (mg/dl)	11.2±2.5	11.2±2.7	0.94
Calcium (mg/dl)	9.8±0.7	9.8±0.5	0.74
Phosphorus (mg/dl)	5.0±1.2	5.5±0.8	0.20
Parathyroid hormone (pg/ml)	464.9±460.4	938.0±878.3	0.07
Albumin (g/dl)	4.2±0.4	4.3±0.4	0.54
Ferritin (ng/ml)	773.1±873.4	346.3±476.4	0.18
TSAT (%)	30.9±16.6	31.8±21.4	0.90
Weekly Kt/V_{urea}	6.1±1.8	6.1±1.5	0.91

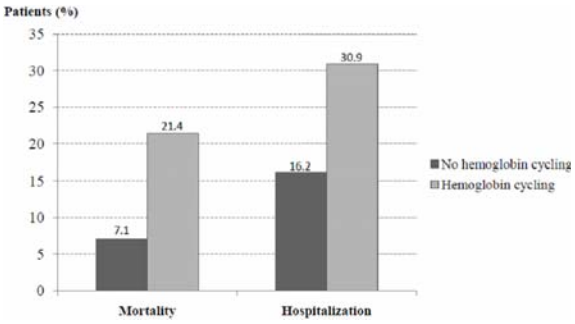

Fig. 2 Mortality and hospitalization rates of patients with and without hemoglobin cycling (OR for mortality = 2.51; 95% CI: 0.31-20.17, p = 0.70 and OR for hospitalization = 1.65; 95% CI: 0.43-6.18, p = 0.56).

fluctuation in accordance with the system described by Ebben et al[14], the mortality rates of patients in LOW, LAL, HA were 20.0, 13.8, and 16.3%, respectively, p = 0.77). The hospitalization rates were 35.0, 25.3, and 37.2%, respectively, p = 0.33), which shows that the mortality and hospitalization rates among these three patterns of hemoglobin fluctuation were not significantly different.

Discussion

Prevalence of hemoglobin cycling

Since the introduction of ESA, and the NKF-K/DOQI and ERBP guidelines for hemoglobin targets recommending a range of 11-12 g/dl in all patients with CKD[5,6], the average hemoglobin levels in CKD patients have steadily increased, and recently 15-20% of maintenance dialysis patients had average hemoglobin levels of less than 11 g/dl[16]. However, a 2-year study by Ofsthun et al[17] showed that of 41,919 dialysis patients, more than 50% spent 1.2 to 6 months at hemoglobin levels of <11 g/dl. In addition, a survey by Lacson et al[8] showed that 62% of hemodialysis patients receiving ESA had hemoglobin levels over or under the target range of 11-12 g/dl, while only just over one-third (38%) of patients had hemoglobin within the target range. Furthermore, one retrospective study in the Netherlands found that no patients remained within the target range of 11-12 g/dl over a one-year period during ESA therapy[18]. This is similar to the findings of the present study in which only 11.3% of patients had their mean hemoglobin values in the target range of 11-12 g/d: most (87.3%) had hemoglobin values lower than 11 g/dl, and only a few patients (1.3%) had hemoglobin values higher than 12 g/dl (Fig. 1).

The standard deviation of hemoglobin in maintenance dialysis patients in the United States has been reported to be 1.1 to 1.3 g/dl[16], which may explain the relatively high occurrence of hemoglobin levels outside the recommended range of 11-12 g/dl. This suggests that many patients who receive ESA experience fluctuations in hemoglobin over time, and this has been shown in a number of studies such as the one by Fishbane et al[7], in which it was found that more than 90% of their patients experienced hemoglobin cycling. Surprisingly, it was also demonstrated in the present study that 90.7% of patients experienced it. The mean amplitude per hemoglobin excursion and the mean duration of hemoglobin cycling were in close agreement with the reported study[7]. However, the annual mean number of incidences of hemoglobin cycling per patient (0.7$\pm$0.4 cycle/patient/year) was lower.

Consequences of hemoglobin cycling

Under normal homeostasis, steady hemoglobin levels are maintained to ensure consistent and adequate oxygen delivery to tissues. Hemoglobin cycling is actually a normal natural event, and a healthy human's hemoglobin may vary by nearly 1 g/dl over a year without clinical significance[19]. In CKD patients, one would expect greater variability in hemoglobin cycling than in healthy persons because of various hemodialysis-related factors such as blood loss, iron deficiency, fluid status, and infections. Additionally, treatment with EPO differs greatly from normal erythropoietin biology. The ESA drugs are administered intermittently, resulting in great fluxes in serum erythropoietin levels, and in turn, fluctuations in hemoglobin. It has been suggested that fluctuations in hemoglobin or hemoglobin cycling, may lead to variability in oxygen delivery to tissues, therefore resulting in end-organ damage[20]. The myocardium may be predominantly vulnerable to hemoglobin variability because it compensates for periods of reduced oxygen delivery with increased output and myocardial cell growth. The results may be repeated activation and resetting of cardiac growth signals, and the development of pathologic changes such as left ventricular dilation or hypertrophy[20]. In addition, the autonomic nervous system may also be susceptible to hemoglobin variability, and it has been confirmed as a potential risk factor for sudden death[9].

Hemoglobin cycling or fluctuations in serum hemoglobin has been linked to poor patient outcomes and is independently associated with higher

mortality[2], and it has been shown in a number of studies to be associated with augmented risk of hospitalization and mortality[10,21,22]. Greater variability in hemoglobin levels is itself associated with adverse outcomes. A retrospective survival analysis of 34,963 chronic hemodialysis patients showed that each 1-g/dl increase in the standard deviation of hemoglobin levels was related to a 33% increase in the rate of annual mortality (95% CI: 22-45)[9]; in other words, each 1-g/dl increase in hemoglobin variability was related to an adjusted hazard ratio for all-cause mortality of 1.93 (95% CI: 1.20-3.10)[21]. In the present study, although there were no significant differences in the mortality and hospitalization rates of patients with hemoglobin cycling and those without it, for patients with hemoglobin cycling, there was a trend towards increased mortality rates (15.3% vs. 7.1%; OR = 2.51, 95% CI: 0.31-20.17, $p = 0.70$) and a tendency towards increased rates of hospitalization (30.0% vs. 21.4%; OR = 1.65, 95% CI: 0.43-6.18, $p = 0.56$). One reason for the inability to demonstrate a significant difference in the present study may relate to the study design and its primary objective, which was to determine the prevalence of hemoglobin cycling; this may have resulted in too few patients being in the group without hemoglobin cycling.

Besides the effect of hemoglobin cycling occurrence on adverse clinical outcomes, the patterns of hemoglobin variability also have similar impacts. Ebben et al[14] characterized six different types of hemoglobin variability patterns and found that patients with consistently low hemoglobin levels had the highest percentage of hospitalizations and co-morbidities. Persistently or transiently low hemoglobin levels have also been shown to be associated with hospitalization and death, as have downward hemoglobin excursions[23]. In a number of recent observational studies, a U-shaped or inverse J-curve relationship was observed between hemoglobin levels and clinical outcomes[24]. Similarly, a recent retrospective study of 58,058 maintenance hemodialysis patients also showed an inverse J-curve relationship between hemoglobin levels and adverse outcomes[23]. In the present study, when stratifying the patterns of hemoglobin fluctuation in accordance with the system described by Ebben et al[14], although the mortality and hospitalization rate of patients in LOW, LAL, HA were not significantly different, it could be shown that the mortality and hospitalization rates were lower in the group with LAL (13.8% and 25.3% respectively), than in HA (16% and 37.2%) and LOW (20% and 35%).

Factors affecting hemoglobin cycling

It has been reported that possible contributors to hemoglobin variability in patients with CKD include ESA-related factors (types, routes of administration), demographics and clinical status (age, pre-existing co-morbid conditions), iron deficiency, infections, inflammation, malignancy, practice pattern (guideline) and reimbursement-related factors (reimbursement policies and regulations)[24]. Other reasons for hemoglobin variability include acute/chronic co-morbidities, blood loss or transfusion, dialysis treatment features such as dialysis adequacy, water quality, level of PTH, vitamin status, and alteration of nutritional status[26].

Hospital admission is frequently associated with infectious and inflammatory conditions that increase resistance to the effects of ESA; furthermore, emergency admission may sometimes lead to missed ESA doses[7]. Therefore, it is likely that hemoglobin fluctuation is an indicator rather than a cause of intercurrent illness. Such an understanding would be supported by the strong associations between hemoglobin cycling and both infection and hospitalization[14]. In the present study, although the authors demonstrated a pattern of increased hospitalization in patients with hemoglobin cycling, the exact causes of hospitalization were not available. Dose adjustment of ESA may be one of the main causes of hemoglobin fluctuations. Frequent ESA dose changes were required to maintain hemoglobin levels within the target range of 11-12 g/dl as recommended in the NKF-K/DOQI guidelines[5,12]. Setting a narrow hemoglobin target range may increase the opportunities for observing actual hemoglobin levels that deviate out of range, causing clinicians to respond to hemoglobin fluctuations outside the target range with a change in ESA dose and trying to return the hemoglobin back to the target range again. As a result, the average ESA dose change has been reported to be 6.3 dose changes/patient/year[7], which is close to the findings in the present study. However, the authors could not demonstrate a significant difference between patients with hemoglobin cycling and those without it (7.2 ± 2.4 vs. 8.2 ± 1.7 dose changes/patient/year respectively, $p = 0.14$).

Besides the practice patterns of anemia management, which in turn are influenced by clinical practice guidelines, hemoglobin variability is also affected by treatment protocols and reimbursement policies[25]. The Thailand Renal Replacement Therapy Registration during the period of study reported in

2010[26] that over one-third of hemodialysis patients (37%) were supported by the Social Security fund or the National Health Security Office fund. This was true for patients in the present study; over 50% of them were supported by these funds, which strictly regulate ESA dosing schedules by using inflexible ESA dose adjustment protocols, which do not account for patient-specific responsiveness, and this might be insufficient to maintain a proper hemoglobin level[20].

Types of ESA with different durations of action may have had an influence on the occurrence of hemoglobin cycling. Whether extended versus shorter dosing intervals with any of these ESA agents are related to less variability in hemoglobin levels remains to be confirmed in clinical trials. Short-acting ESA, which has a relatively short half-life (the mean half-lives of both epoetin-alfa or epoetin-beta are less than 24 hours), requires administration as often as twice or three times a week. Darbepoetin which has a rather longer half-life than epoetin alfa or beta (about 25 hour compared to <9 hour) and is routinely used once a week, has been used effectively for once-monthly dosing in stable dialysis patients[27,28]. It has also been reported that darbepoitin can achieve better hemoglobin stability than short-acting ESA[29].

CERA, a continuous erythropoietin receptor activator, with a long half-life (approximately 130 hours), provides anemia correction with more stable maintenance of hemoglobin levels at extended administration intervals in CKD patients. Subcutaneous CERA once or twice monthly has been shown to successfully maintain tight and stable hemoglobin levels in dialysis patients[30]. A study in peritoneal dialysis patients showed effective achievement of hemoglobin stability with once-monthly CERA, and promisingly, the maximum intra-individual fluctuation of $\leq$1 g/dl was shown in 85.4% of patients[31].

Finally, it seems that minimizing hemoglobin cycling or variability can have significant short- and long-term clinical consequences. Fewer fluctuations above 12 g/dl may minimize the occurrence of serious cardiovascular events associated with high hemoglobin levels, while fewer fluctuations below 11 g/dl may provide improved symptomatic relief and increased survival. Improved hemoglobin stability also results in better performance. Importantly, individualized anemia management may reduce hemoglobin cycling in hemodialysis patients, as suggested by the findings of a study by Gaweda et al[32].

The present study has some limitations; most importantly, the design was retrospective, which precludes determination of causality between hemoglobin fluctuations and most of the associated factors.

Conclusion

In the present study, the authors found that hemoglobin cycling was common in Thai hemodialysis patients treated with ESA. Although it did not significantly affect the mortality and hospitalization rates, there was a pattern of increasing mortality and hospitalization. The authors propose that using more extended-acting ESA or individualized ESA dose adjustment may be a key factor in reducing hemoglobin-cycling occurrence in hemodialysis patients.

What is already known on this topic ?

Hemoglobin cycling is common among end-stage renal disease patients, who receive chronic maintenance hemodialysis, are treated with erythropoietin.

The influence of hemoglobin cycling on mortality is still equivocal.

Some risk factors for hemoglobin cycling have been proposed.

What this study adds ?

Hemoglobin cycling in ESRD patients has never previously been studied in Thailand.

Prevalence of hemoglobin cycling in Thai ESRD patients.

The adverse influence of hemoglobin cycling cannot be confirmed.

ESA treatment by treatment protocol or reimbursement policies may not be appropriate for all patients.

Individualized anemia management and more extended-acting ESAs are proposed for keeping more stable hemoglobin levels.

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Potential conflicts of interest

None.

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ความชุกของ Hemoglobin Cycling และผลกระทบทางคลินิกในผู้ป่วยโรคไตวายเรื้อรังระยะท้ายที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมและได้รับยา Erythropoiesis-Stimulating Agent

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ภูมิหลัง: Erythropoiesis-stimulating agent (ESA) เป็นยาหลักที่ใช้ในการรักษาภาวะโลหิตจางในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียม ผู้ป่วยเหล่านี้มักเกิดปรากฏการณ์การแกว่งขึ้นลงของระดับฮีโมโกลบินที่เรียกว่า hemoglobin cycling ซึ่งพบว่าอาจมีความสัมพันธ์กับอัตราการเสียชีวิตของผู้ป่วย

วัตถุประสงค์: เพื่อประเมินความชุกของภาวะ hemoglobin cycling ในผู้ป่วยไทยที่เป็นโรคไตวายเรื้อรังระยะท้ายที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมและได้รับยา ESA และวิเคราะห์ว่าภาวะดังกล่าวจะมีผลกระทบต่อผลลัพธ์ทางคลินิกอย่างไร ตลอดจนการหาปัจจัยเสี่ยงต่อการเกิดภาวะดังกล่าว

วัสดุและวิธีการ: เป็นการศึกษาเชิงวิเคราะห์แบบย้อนหลัง (analytic retrospective study) ในผู้ป่วยโรคไตวายเรื้อรัง 150 ราย ที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมและได้รับการรักษาด้วยยา ESA ที่โรงพยาบาลราชวิถีและมูลนิธิโรคไตแห่งประเทศไทย ณ ตึกกัลยาณิวัฒนา โรงพยาบาลสงฆ์ ระหว่างปี พ.ศ. 2551 ถึง พ.ศ. 2553 โดยกำหนดว่าเกิด hemoglobin cycling เมื่อมีช่วงการแกว่งขึ้นหรือลงของระดับฮีโมโกลบินเป็นเวลานานตั้งแต่ 8 สัปดาห์ขึ้นไปและมี amplitude ในการแกว่งของฮีโมโกลบินมากกว่า 1.5 กรัม/ดล.

ผลการศึกษา: พบความชุกของ hemoglobin cycling ร้อยละ 90.7 ของผู้ป่วยโดยมีค่าเฉลี่ยของ amplitude 2.4±0.7 กรัม/ดล. ระยะเวลาเฉลี่ยของ 1 hemoglobin cycling นาน 8.5±5.0 สัปดาห์ ผู้ป่วยส่วนใหญ่ (ร้อยละ 34.7) เกิด hemoglobin cycling 2 ครั้ง ระดับฮีโมโกลบินเฉลี่ยของกลุ่มที่มี hemoglobin cycling (กลุ่มที่ 1) และไม่มี hemoglobin cycling (กลุ่มที่ 2) เป็น 10.1±0.9 กรัม/ดล. และ 10.2±0.7 กรัม/ดล. ตามลำดับ (p = 0.597) มีค่าความเสี่ยง (odd ratio) ของอัตราการเสียชีวิตและการนอนโรงพยาบาลของกลุ่มที่ 1 เมื่อเทียบกลับกลุ่มที่ 2 เป็น 2.52 (95% CI: 0.31-20.27, p = 0.700) และ 1.65 (95% CI: 0.43-6.18, p = 0.560) ตามลำดับ จำนวนครั้งของในการปรับขนาด ESA ในกลุ่มที่ 1 และ 2 ไม่แตกต่างกัน (7.2±2.4 vs. 8.2±1.7 ครั้งต่อผู้ป่วยต่อปี, p = 0.14) ผลการตรวจเลือดเพื่อประเมินระดับ blood urea nitrogen, creatinine, intact parathyroid hormone, ferritin, % transferrin saturation, weekly Kt/V_{urea} ไม่แตกต่างกัน รวมทั้งโรคร่วมต่างๆ ของผู้ป่วย (ได้แก่ เบาหวาน ความดันโลหิตสูง โรคหัวใจล้มเหลว และโรคหลอดเลือดสมอง) ก็ไม่แตกต่างกัน

สรุป: Hemoglobin cycling พบได้บ่อยในผู้ป่วยไทยที่เป็นโรคไตวายเรื้อรังระยะท้ายที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมและได้รับยา ESA จากการศึกษานี้ไม่สามารถแสดงให้เห็นว่าภาวะ hemoglobin cycling มีผลต่ออัตราการเสียชีวิตและอัตราการนอนโรงพยาบาล แต่มีแนวโน้มของการเพิ่มความเสี่ยงต่อการเสียชีวิตและการนอนโรงพยาบาล