# Factors Related to Erythropoietin Hyporesponsiveness in Peritoneal Dialysis Patients with Anemia

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***Background:*** *Anemia in peritoneal dialysis (PD) patients can be improved after treatment with erythropoietin (EPO). However, several factors previously reported can cause EPO hyporesponsiveness including nutritional deficiency, infection or inflammation, secondary hyperparathyroidism with bone marrow fibrosis, angiotensin converting enzyme inhibitor (ACEI) administration, and dialysis inadequacy. Correction of these factors may lower doses and costs of EPO for these patients.*
***Objective:*** *To calculate the prevalence of EPO hyporesponsiveness and the associated factors in PD patients with anemia.*
***Material and Method:*** *We reviewed medical records of 195 PD patients who received EPO treatment during January 2000 to June 2013.The doses of EPO were titrated maximally to 8,000 U/week to maintain a target Hematocrit (Hct) level between 33% and 36%. PD patients Hct less than 30% before and after EPO administration for 3 months were included in this study. There were 44 patients who were recruited by the criteria. They had no history of bleeding or red cell transfusions within 2 months. The EPO resistance index (ERI) was calculated as weekly EPO doses per Hct levels per kilograms body weight (kg). The EPO hyporesponsiveness was defined as the weekly EPO doses was ≥150 U/kg. The relationship between the ERI and continuous parameters was calculated by the student's t-test. Chi-square and Fisher's exact correlation were performed to analyze the relationship between ERI and categorical variables. The p-value <0.05 was considered statistically difference.*
***Results:*** *There were 13 (6.7%) patients having Hct less than 33% after the administration EPO ≥150 U/kg/week for 3 months. The statistically significant relationship between ERI and gender was detected. Female had higher rate of having EPO hyporesponsiveness (p = 0.02).*
***Conclusion:*** *The prevalence of EPO hyporesponsiveness was 6.7%. Female gender was a factor related to EPO hyporesponsiveness in our study.*

***Keywords:*** *Erythropoietin, Anemia, Peritoneal dialysis, Chronic kidney disease*

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Anemia is a common problem in peritoneal dialysis (PD) patients. Erythropoietin (EPO) has been used to treat anemic PD patients since the 1980s[1]. Anemia in the majority of patients has shown improvement after the EPO administration[2-7]. It has been reported that 90-95% of patients have good response to EPO in large multicenter trials. However, there are 5-10% of patients shown a poor response to EPO[8-10]. Factors leading to EPO hyporesponsiveness include iron deficiency anemia[11] (both absolute and functional iron deficiency), blood loss, vitamin B12 deficiency, folate deficiency[4], and aluminum toxicity[12]. The increased levels of serum parathyroid hormone (PTH) which can inhibit erythropoiesis are reported in the in vitro studies[12-14]. It can be the cause of EPO hyporesponsiveness[15,16]. Acute and chronic inflammation cause EPO poor response[17,18]. Others studies have reported that high levels of C-reactive protein (CRP)[16,19], low serum albumin, lower normalized protein catabolic rate (nPCR)[16], the use of angiotensin converting enzyme inhibitor (ACEI)[20], and the low weekly Kt/V of urea[21,22] can be the causes of EPO hyporesponsiveness.

The National Health Security of Thailand has used PD first as the mode of dialysis for patients who are under the universal health coverage (UC) scheme. EPO administration in these patients will be provided

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according to Hct levels lower than 30%. The maximum dosage of EPO per patient will be limited to 8,000 U per week. The objective of this study is to investigate the prevalence and factors associated with the EPO hyporesponsiveness. If these factors are corrected, the doses of EPO can be reduced. This will be of the benefit to the fiscal budget providing EPO to these patients.

**Material and Method**

This was a retrospective cohort study. We reviewed the records of 195 PD patients at the HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University, Nakhon Nayok, Thailand from January 2000 to June 2013. Patients with hematocrit (Hct) less than 30% received EPO which would be titrated according to their Hct level to maintain a target Hct level between 33% and 36%. The maximum EPO dosage per patient was limited to 8,000 U per week. The inclusion criteria for selecting subjects were age over 18 years old, performing PD for at least 3 months, without history of receiving red cell transfusions and history of blood loss within the last 2 months, and having Hct less than 30% before and after receiving EPO regularly for 3 months. Oral iron was administered to maintain transferrin saturation (TSAT) and ferritin levels higher than 20% and 100 ng/mL, respectively. The variables at the time of PD initiation and at the follow-up periods collected for analyses were age, gender, occupation, underlying disease, cause of end stage renal disease (ESRD), PD prescription, body weight, complete blood count, residual renal function, serum albumin, serum calcium, serum phosphorus, weekly total KT/V of urea, and weekly total creatinine clearance. The EPO doses per week in the patients with Hct less than 30% were calculated. The EPO resistance index (ERI) was defined as weekly EPO doses per Hct level per kilograms of body weight. Patients received the EPO dose $\geq$150 U/kg/week were classified as the EPO hyporesponsiveness[10,16]. The collected variables were analyzed to investigate factors associated with the EPO hyporesponsiveness.

***Statistical methods***

The descriptive data were reported in percentage and mean $\pm$ standard deviation (SD). The relationship between the ERI and the continuous variables were analyzed by student's t-test. The relationship between the ERI and the categorical variables were performed by Chi-square and Fisher's exact correlation. The $p$-value <0.05 was considered statistically significant difference.

**Results**

There were 44 patients with Hct less than 30% before and after the EPO administration for a duration of 3 months. These patients had the mean of age 53.9 years. The numbers of males and females were 29 (66%) and 15 (34%), respectively. Thirty-one (70.5%) patients were under the universal health coverage scheme. The most common cause of ESRD in our patients was diabetic nephropathy (25 patients, 56.8%) followed by long standing hypertension (8 patients, 18.2%). There were 1 (2.3%), 4 (9.1%) and 7 (15.9%) patients with ESRD from chronic glomerulonephritis, others, and unknown causes, respectively. Other characteristics and laboratory findings are shown in Table 1.

The characteristics and laboratory of PD patients with EPO <150 U/kg/week and those with EPO $\geq$150 U/kg/week are shown in Table 2. There were 13 (29.5%) from 44 patients who received EPO dose $\geq$150 U/kg/week. The prevalence of the EPO hyporesponsiveness was 6.7%. The ERI had a statistically significant correlation with patients who were of the female gender ($p$ = 0.02). Other factors including age, serum calcium, serum phosphate, serum albumin, TSAT, ferritin, weekly KT/V, the use of ACEI, serum PTH, and peritonitis were not found to have statistically significant association with the ERI.

**Discussion**

Previous studies have shown that there are

**Table 1.** Characteristics and laboratory results of 44 PD patients with Hct less than 30% after EPO administration for 3 months

| Characteristics and laboratory | Mean $\pm$ SD |
|---|---|
| Age at the time start PD (years) | 53.9$\pm$15.7 |
| Hb level (g/dL) | 8.9$\pm$0.8 |
| MCV (fL) | 82.5$\pm$9.9 |
| Calcium (mg/dL) | 8.4$\pm$0.8 |
| Phosphorus (mg/dL) | 5.21$\pm$2.1 |
| Albumin (g/L) | 2.75$\pm$0.6 |
| Parathyroid hormone (pmol/L) | 197.4$\pm$102.3 |
| Transferrin saturation (%) | 30.8$\pm$16.9 |
| Ferritin (ng/ml) | 633.7$\pm$433.7 |
| Erythropoietin (dose unit/wk) | 7,351.1$\pm$2,085.8 |
| Erythropoietin unit/kg/week | 127.9$\pm$49.3 |
| Total weekly creatinine clearance (L) | 58.4$\pm$23.8 |
| Total weekly Kt/V (urea) | 1.9$\pm$0.5 |
| Number of patients with ACEI use (%) | 32 (72.7) |
| Number of patients with peritonitis (%) | 5 (88.6) |

**Table 2.** Characteristics and laboratory of PD patients with EPO <150 U/kg/week and EPO ≥150 U/kg/week

| Parameter | Patients with EPO <150 U/kg/week (n = 31) | Patients with EPO ≥150 U/kg/week (n = 13) | *p*-value |
|---|---|---|---|
| Age (years) | 52.0±14.0 | 58.5±17.4 | 0.3 |
| Gender (%) | | | |
| Male | 24 (77.4) | 5 (38.5) | |
| Female | 7 (22.6) | 8 (61.5) | 0.02 |
| Diabetes (%) | 13 (41.9) | 8 (61.5) | 0.3 |
| Calcium (mg/dL) | 8.37±0.82 | 8.39±0.74 | 0.9 |
| Phosphorus (mg/dL) | 5.38±2.36 | 4.77±0.82 | 0.2 |
| Albumin (g/L) | 2.79±0.54 | 2.62±0.56 | 0.4 |
| Parathyroid hormone (pmol/L) | 211.90±96.76 | 166.79±112.74 | 0.3 |
| TSAT (%) | 29.37±17.04 | 33.12±17.19 | 0.6 |
| Ferritin (ng/ml) | 568.10±416.03 | 746.85±460.05 | 0.3 |
| Total weekly Kt/V | 1.88±0.53 | 1.91±0.60 | 0.9 |
| ACEI use (%) | | | |
| Yes | 22 (71) | 10 (76.9) | |
| No | 9 (29) | 3 (23.1) | 0.1 |
| Peritonitis (%) | | | |
| Yes | 2 (6.5) | 3 (23.1) | |
| No | 29 (93.5) | 10 (76.9) | 0.1 |

The *p*-value = student t-test for continuous variable, Chi-square and Fisher's exact for categorical variable

several factors related to EPO hyporesponsiveness. These factors are infection or inflammation[16-19], nutritional deficiency[4,11], secondary hyperparathyroidism with marrow fibrosis[15,16], ACEI administration[20], and dialysis inadequacy in terms of KT/V[11-21]. We used an EPO dose of 150 U/kg/week as a cut off value to define the ERI and the EPO hyporesponsiveness[10,16]. The EPO hyporesponsiveness is found in 5-10% of studies from multicenters[8-10]. The percentage of EPO hyporesponsiveness in our study was 6.7% (13 from 195 patients) which was similar to the previous report.

Our study has shown that female had higher rate of EPO hyporesponsiveness than male ($p = 0.02$). The possible explanation might be the lack of androgenic hormone in the female. Androgen can stimulate erythropoiesis by increasing the number of erythropoietin-responsive cells, increasing bone marrow activity and increasing iron incorporation into red cells[23,24]. There is a study demonstrating the relationship between EPO hyporesponsiveness and low potentiated in ESRD patients supplemented with androgen[25]. Low serum albumin[10,16,26], high levels of serum PTH[15,16,27], inflammation or infection factors[16-19], the use of ACEI[20], the low Kt/V[21,22] was not found in our study. These may result from a small number of patients in our study.

One limitation in our study is lacking the data of hemoglobin typing and DNA analysis to determine if our patients had thalassemia minor which may indicate a poor response to EPO. Thalassemia is a common disease in Thailand, therefore, it may be a factor associated with EPO hyporesponsiveness in our studied group. Since gender is an only factor found to be associated with the EPO hyporesponsiveness in this study and it is an unchangeable factor, the results may not have any impact on the policy in the aspect of the limitation of the maximum dosage of EPO. The hypothesis that PD female patients having higher risk of the EPO hyporesponsiveness due to lack of androgen should be further investigated. If the hypothesis is right, it can be corrected by supplemental androgenic hormone. The other limitation of this study is the small number of subjects.

## Conclusion

The prevalence of EPO hyporesponsiveness is 6.7% which is similar to other studies. Being of the female gender is a factor associated with the EPO hyporesponsiveness in our study.

## What is already known on this topic?

There are several factors related to EPO hyporesponsiveness.

**What this study adds?**

We have found that being of the female gender is associated with EPO hyporesponsiveness.

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**Potential conflicts of interest**

None.

**References**

1. Eschbach JW, Adamson JW. Recombinant human erythropoietin: implications for nephrology. Am J Kidney Dis 1988; 11: 203-9.
2. Icardi A, Paoletti E, Molinelli G. Efficacy of recombinant erythropoietin after subcutaneous or intraperitoneal administration to patients on CAPD. Adv Perit Dial 1990; 6: 292-5.
3. Macdougall IC, Davies ME, Hutton RD, Cavill I, Lewis NP, Coles GA, et al. The treatment of renal anaemia in CAPD patients with recombinant human erythropoietin. Nephrol Dial Transplant 1990; 5: 950-5.
4. Humphries JE. Anemia of renal failure. Use of erythropoietin. Med Clin North Am 1992; 76: 711-25.
5. Lai PC, Wu MS, Huang JY, Huang CC, Leu ML. Efficacy of intravenous and subcutaneous erythropoietin in patients on hemodialysis and continuous ambulatory peritoneal dialysis. Changgeng Yi Xue Za Zhi 1994; 17: 105-12.
6. Stenver DI, Nielsen B. Erythropoietin treatment of dialysis patients. Ugeskr Laeger 1994; 156: 2589-91.
7. Nissenson AR. Erythropoietin treatment in peritoneal dialysis patients. Perit Dial Int 1994; 14 (Suppl 3): S63-9.
8. Eschbach JW, Downing MR, Egrie JC, Browne JK, Adamson JW. USA multicenter clinical trial with recombinant human erythropoietin (Amgen). Results in hemodialysis patients. Contrib Nephrol 1989; 76: 160-5.
9. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med 1987; 316: 73-8.
10. Macdougall IC. Poor response to erythropoietin: practical guidelines on investigation and management. Nephrol Dial Transplant 1995; 10: 607-14.
11. Jonnalagadda V, Bloom EJ, Raja RM. Importance of iron saturation for erythropoietin responsiveness in chronic peritoneal dialysis. Adv Perit Dial 1997; 13: 113-5.
12. Grutzmacher P, Ehmer B, Messinger D, Kulbe KD, Scigalla P. Effect of aluminum overload on the bone marrow response to recombinant human erythropoietin. Contrib Nephrol 1989; 76: 315-21.
13. Meytes D, Bogin E, Ma A, Dukes PP, Massry SG. Effect of parathyroid hormone on erythropoiesis. J Clin Invest 1981; 67: 1263-9.
14. Hampl H, Riedel E, Wendel G, Stabell U and Kessel M. Influence of parathyroid hormone on exogenous erythropoietin stimulated erythropoietin in hemodialysis patients [abstract]. Kidney Int 1988; 33: 224.
15. Al Hilali N, Al Humoud H, Ninan VT, Nampoory MR, Puliyclil MA, Johny KV. Does parathyroid hormone affect erythropoietin therapy in dialysis patients? Med Princ Pract 2007; 16: 63-7.
16. Wei M, Bargman JM, Oreopoulos DG. Factors related to erythropoietin hypo-responsiveness in patients on chronic peritoneal dialysis. Int Urol Nephrol 2007; 39: 935-40.
17. Pilkey RM, Morton AR, Iliescu EA. Inflammation, peritoneal transport, and response to erythropoietin in peritoneal dialysis patients. Adv Perit Dial 2001; 17: 153-7.
18. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. Lancet 1986; 2: 1175-8.
19. Kim JK, Park BS, Park MJ, Choi W, Ma SK, Nah MY, et al. The predictive parameters of erythropoietin hyporesponsiveness in patients on continuous ambulatory peritoneal dialysis. Korean J Intern Med 2001; 16: 110-7.
20. Nakamoto H, Kanno Y, Okada H, Suzuki H. Erythropoietin resistance in patients on continuous ambulatory peritoneal dialysis. Adv Perit Dial 2004; 20: 111-6.
21. Opatrna S, Opatrny K Jr. Renal anemia and the effect of long-term dialysis. Cas Lek Cesk 1999; 138: 107-10.
22. Lo WK, Ho YW, Li CS, Wong KS, Chan TM, Yu AW, et al. Effect of Kt/V on survival and clinical

outcome in CAPD patients in a randomized prospective study. Kidney Int 2003; 64: 649-56.
23. Shahani S, Braga-Basaria M, Maggio M, Basaria S. Androgens and erythropoiesis: past and present. J Endocrinol Invest 2009; 32: 704-16.
24. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 2008; 93: 914-9.
25. Ballal SH, Domoto DT, Polack DC, Marciulonis P, Martin KJ. Androgens potentiate the effects of erythropoietin in the treatment of anemia of end-stage renal disease. Am J Kidney Dis 1991; 17: 29-33.
26. Gunnell J, Yeun JY, Depner TA, Kaysen GA. Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 1999; 33: 63-72.
27. Drueke TB. R-HuEPO hyporesponsiveness—who and why? Nephrol Dial Transplant 1995; 10 (Suppl 2): 62-8.

## *ปัจจัยที่มีผลลดการตอบสนองต่อยาอีรีโทรพอยอีตินในผู้ป่วยที่ได้รับการล้างไตทางช่องท้องที่มีภาวะโลหิตจาง*

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***ภูมิหลัง:*** *ภาวะโลหิตจางเป็นภาวะที่พบได้บ่อยในผู้ป่วยที่ล้างไตทางช่องท้อง ผู้ป่วยที่ได้รับยาอีรีโทรพอยอีตินจะทำให้ภาวะโลหิตจางดีขึ้น ปัจจัยที่มีผลต่อการตอบสนองต่อยาอีรีโทรพอยอีตินไม่ดีได้แก่ ภาวะขาดสารอาหาร การติดเชื้อ การอักเสบ ภาวะพาราไธรอยด์สูงทำให้เกิดพังผืดในไขกระดูก การได้รับยา angiotensin converting enzyme (ACEI) และการล้างไตที่ไม่เพียงพอ ถ้าสามารถแก้ไขปัจจัยที่มีผลทำให้การตอบสนองต่ออีรีโทรพอยอีตินลดลงก็จะทำให้ลดขนาดการใช้ยาและค่าใช้จ่ายของยาอีรีโทรพอยอีตินลดลง*

***วัตถุประสงค์:*** *เพื่อศึกษาปัจจัยที่มีผลต่อการตอบสนองต่อยาอีรีโทรพอยอีตินลดลงในผู้ป่วยที่ได้รับการล้างไตทางช่องท้องที่มีภาวะซีด*

***วัสดุและวิธีการ:*** *การดำเนินวิจัยเป็นการศึกษาย้อนหลังเชิงพรรณนาโดยทบทวนเวชระเบียนผู้ป่วยที่ได้รับการล้างไตทางช่องท้องที่ศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี และได้รับยาอีรีโทรพอยอีติน ผู้ป่วยที่มียังมีภาวะซีดหลังได้รับยาอีรีโทรพอยอีติน และไม่มีประวัติสูญเสียเลือดหรือได้รับเลือดภายใน 2 เดือน จะคำนวณการตอบสนองต่อยาอีรีโทรพอยอีตินเป็นขนาดยาอีรีโทพอยอีตินที่ได้รับต่อค่าฮีมาโตรคริทต่อน้ำหนักตัว (EPO dose U/Kg/week) นิยามการตอบสนองต่อยาอีรีโทพอยอีตินไม่ดีคือ ผู้ป่วยที่ยังมีภาวะซีดหลังได้รับยาอีรีโทพอยอีตินในขนาดตั้งแต่ 150 ยูนิต/กิโลกรัม/สัปดาห์เป็นเวลาอย่างน้อย 3 เดือน*

***ผลการศึกษา:*** *ผู้ป่วยล้างไตทางช่องท้องจำนวน 44 คนจากจำนวน 195 คน ได้รับยาฉีดอีริโทรพอยอีตินอย่างสม่ำเสมอและมีค่าฮีมาโตรคริทน้อยกว่า 30% คิดเป็น 22.6% โดยมีผู้ป่วย 13 (6.7%) คนเข้าเกณฑ์การตอบสนองต่อยาอีรีโทพอยอีตินไม่ดี ปัจจัยที่มีผลต่อการตอบสนองต่อยาอีรีโทรพอยอีตินไม่ดีได้แก่ เพศหญิง (p = 0.02)*

***สรุป:*** *การศึกษานี้พบว่าเพศหญิงเป็นปัจจัยสำคัญในผู้ป่วยล้างไตทางช่องท้องที่มีการตอบสนองต่อยาอีรีโทรพอยอีตินไม่ดี*