Latent zinc deficiency and zinc supplementation in hemodialysis patients

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Abstract

The zinc supplementation therapy using Polaprezinc was evaluated for 32 patients undergoing hemodialysis. Their serum zinc concentration was significantly improved(45 to 70μg/dl). Although their anemia level was not significantly changed(10.3 to 10.2 g/dl), the Dolbepoietin α dosage to keep their hemoglobin 10 to 12g/dl was decreased(26.4 to 19.2μg/week). The reduced cost of Darbeopietin was estimated as 20,000Yen per person per year in our facility. The zinc supplementation therapy is effective not only hematopoiesis but also medical economy.

KEY WORDS Zinc supplementation, Polaprezinc, CKD, Hemodialysis patients

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Introduction

Renal anemia is one of the important complications of Chronic Kidney Disease(CKD), especially in patients undergoing hemodialysis[1,2]. In 1980's, recombinant human erythropoietin (rh-EPO)was clinically introduced into therapy for renal anemia in patients with high stage CKD. However, there are still many patients who are suffering from rh-EPO resistant anemia. Recently, Fukushima et al reported the high prevalence of zinc deficient patients undergoing hemodialysis, and also the effect of zinc supplementation for renal anemia[3]. Indeed, hemodialysis patients have been found to have low serum zinc concentration[4,5]. We evaluate here whether the zinc supplementation can improve their serum zinc concentration and also anemia level.

Subjects & Methods

a) Patients

Thirty-two patients with chronic renal failure receiving outpatient maintenance hemodialysis (male : 23, female : 9, mean age : 64. 34 years old)those who were not taking zinc-based agents and supplementation were screened to measure data combined blood count(CBC), biochemical examination and serum levels of zinc and copper.

b) Zinc therapy and improvement of anemia

Thirty-two chronic renal failure patients receiving hemodialysis at Tsushima Izuhara Hospital were randomly divided into two groups. The first group named 'with Zn' is composed of 18 patients(male=12, female=6, mean age=62.5 year-old). The second group named 'without Zn' is consisted of 14 patients(male=11, female=3, mean age=66.7 year-old). Polaprezinc at a dosage of 150mg/day which contains 34mg/day of zinc was administered to 'with' group.

c)Erythropoiesis Stimulating Agents (ESA)

In Tsushima Izuhara Hospital, to control the patients anemia Dorbepoietin alfa(DA)in only used via intra-venous. And in this hospital, the target anemia level is 10 to 12g/dl as their hemoglobin data at post hemodialysis sampling. When their hemoglobin data was over 12g/dl, the DA dosage was reduced as 20μg/weekly.

d) Fe agents

Their data about Fe kinetics including serum Fe concentration, total iron binding capacity (TIBC)and ferritin was measured every month. Transferrin saturation(TSAT)was also calculated as conventional formula. When either TSAT was less than 20% or ferritin was less than 100μg/ml, the Fe supplementation was done. The Fe supplementation was intravenously infused 40mg of saccharated ferric oxide after hemodialysis session one time per week.

e) Laboratory data

Their laboratory data including CBC, Fe kinetics parameters and serum zinc concentration was measured for 6 months. CBC and biochemical data including mineral and renal failure associated data was measured two times per month. Fe kinetics markers were measured once a month. Serum Zn was measured in two points at the beginning and the end of this study. The serum copper level was also investigated in this study because several patients were diagnosed as copper deficiency during zinc supplementation[6].

f) Ethical approval

A following explanation was given to the patients before polaprezinc therapy and consent was obtained in writing; patients required zinc therapy due to zinc deficiency and they were given zinc by using polaprezinc, not for its intended purpose, as gastric ulcer therapy.

g) Questionnaire

We prepared a questionnaire sheet for zinc supplementation therapy. This questionnaire was consisted of five questions.

1) Could you take the tablet of Polaprezinc easily? Yes or No, If your question is No, please write your feeling to take the tablet.
2) Did your wound heal faster than before the treatment? Yes, No or Neither.
3) Did your sense of taste improve? Yes, No or Neither.
4) Did your appetite improved? Yes, No or Neither.
5) If you feel another change in your feeling after taking the tablet, please write.

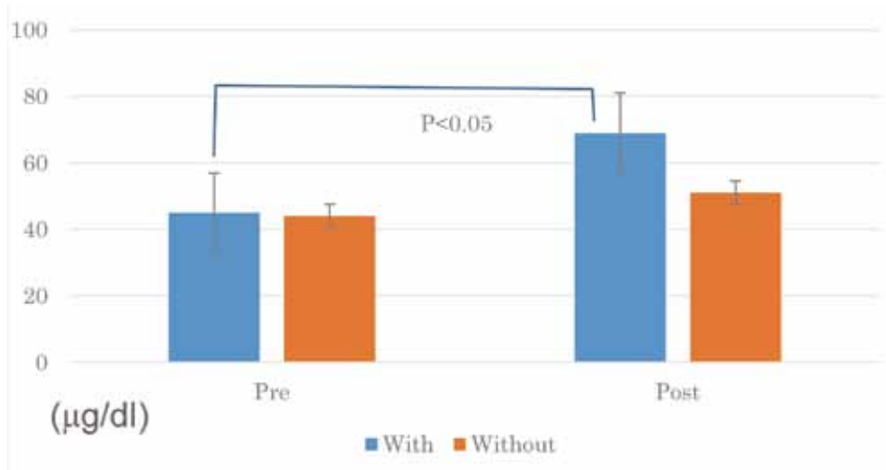

Fig. 1 Serum Zinc concentrations

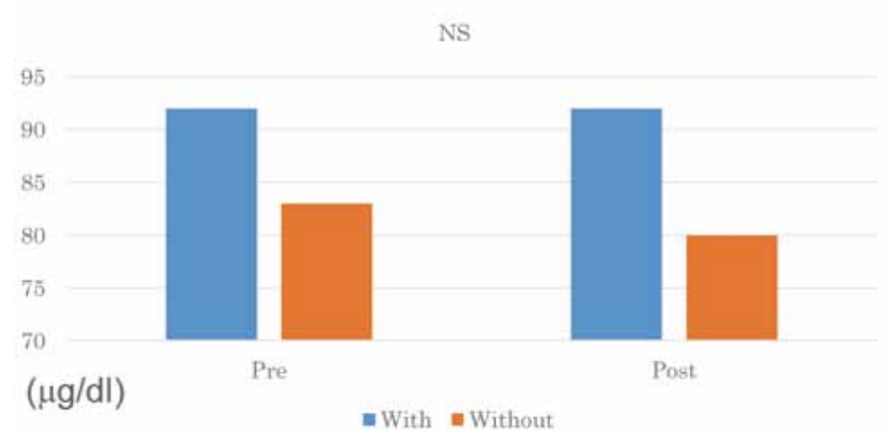

Fig. 2 Serum copper concentrations

Result

a) Zinc concentration(Fig.1)

Fig. 1 shows the changes in the serum zinc concentration at the beginning and the end of zinc supplementation. As seen in figure, serum zinc concentration was elevated 45μg/ml to 75μg/dl ($p<0.05$)in patients with zinc supplementation. In comparison with this, serum zinc concentration was not changed in patients without zinc supplementation(42μg/dl to 43μg/dl).

b) Copper concentration(Fig.2)

Significant change in serum copper concentration was not seen in both groups(with：90 to 89 μg/dl, without：82 to 80μg/dl).

c) Serum Iron level (Fig. 3)

Serum Iron level tended to elevate in 'without Zn' (40 to 50μg/dl, N.S.), though it didn't change significantly in patients with zinc supplementation(39 to 42μg/dl, N.S.). There are more patients with iron supplementation in 'without Zn'than 'with Zn'(with Zn：10/18=55.6%, without Zn 10/14=71.4%, N.S.).

d) Hemoglobin concentration(Fig.4)

Hemoglobin level didn't change in both groups(with 10.3 to 10.2 g/dl, without 10.1 to 10.3 g/dl).

e) Dalbepoietin alpha (DA) dosage(Fig.5)

To control patient's hemoglobin level in the recommended target range 10g/dl to 12g/dl, the necessary DA dosage was 26.4μg/week at the beginning of this study in patients with zinc supplementation. At end of this study, DA dosage in patients with zinc supplementation was decreased to 19.2μg/week. In patients without zinc supplementation, DA dosage was 27.9μg/week at the beginning of this study and declined to 27.9μg/week at the end. The effect of decreasing DA dosage was seen in patient with zinc supplementation. Fig.6 shows the changes of DA dosage. A decrease in DA dosage was mainly seen in first to third month of this study.

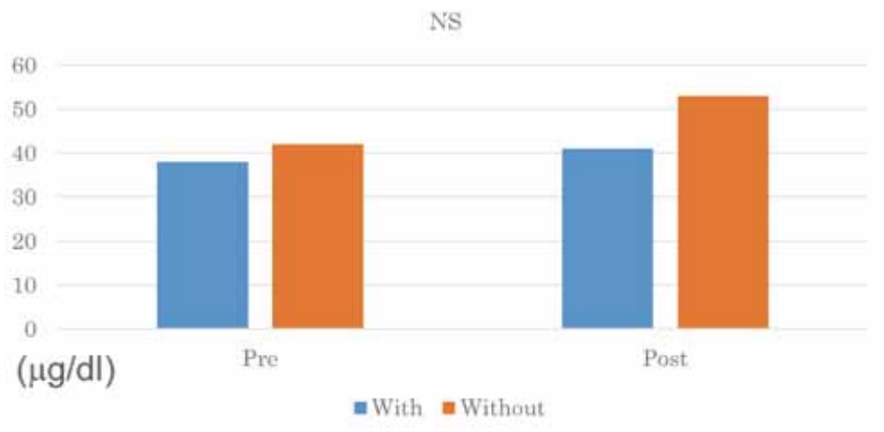

Fig. 3 Serum Iron concentrations

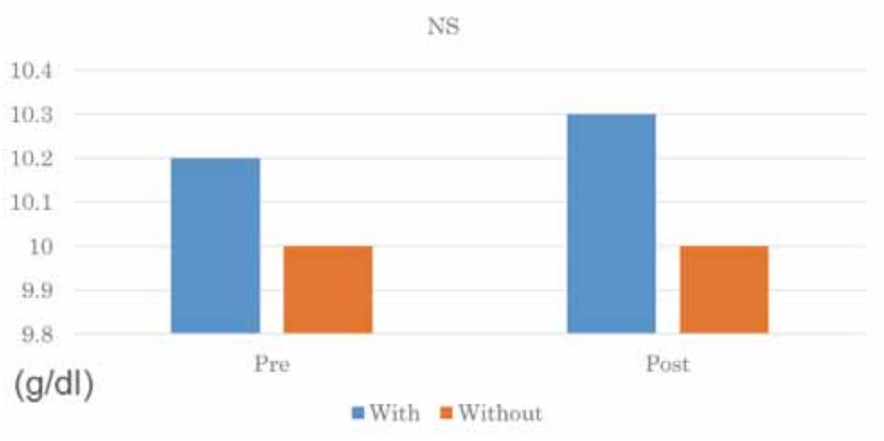

Fig. 4 Hemoglobin concentrations

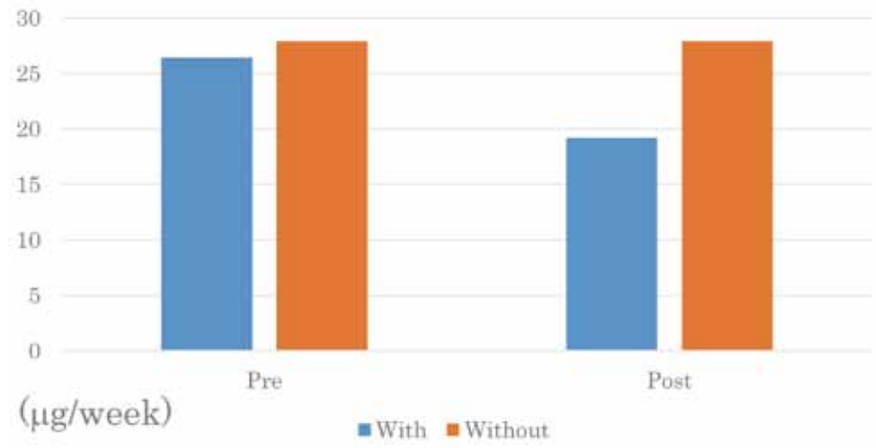

Fig. 5 Darbepoietin α dosages

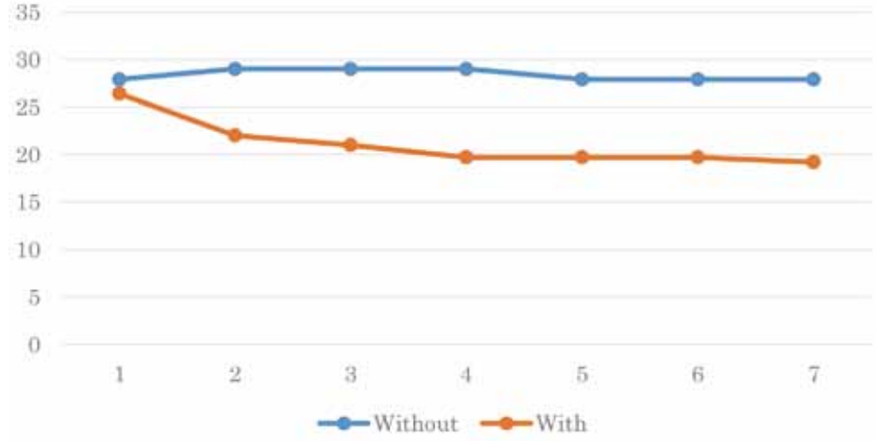

Fig. 6 Changes of dosage of DA

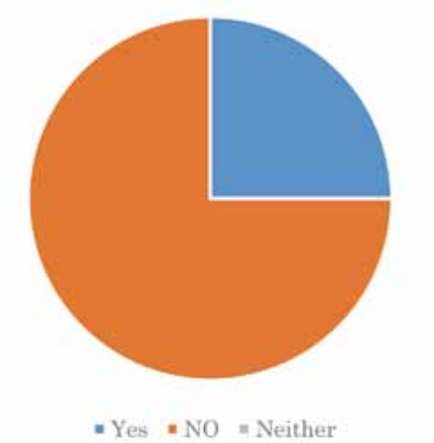

Fig. 7-A Could you feel take Promac tablet easily?

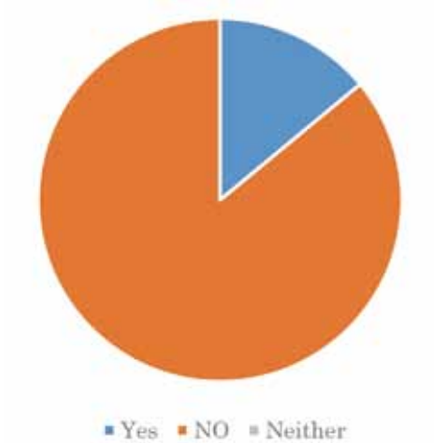

Fig. 7-B Did you feel any changes for your taste?

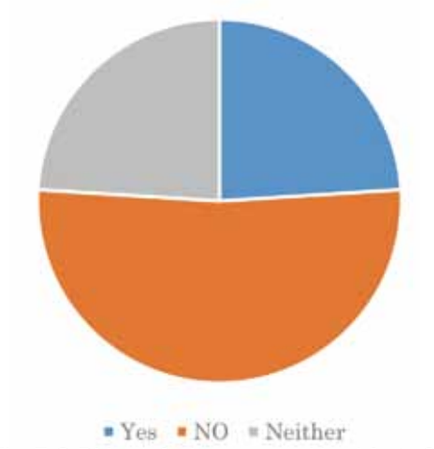

Fig. 7-C Did you feel your wound heal faster?

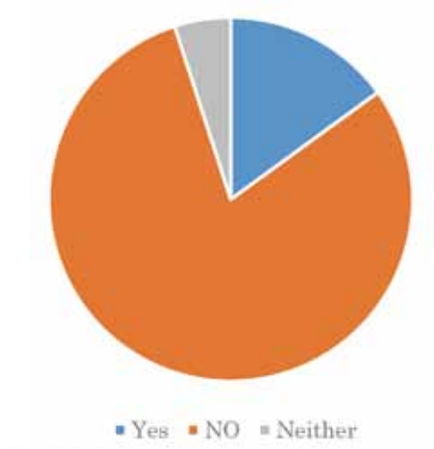

Fig. 7-D Did you feel your appetite improve?

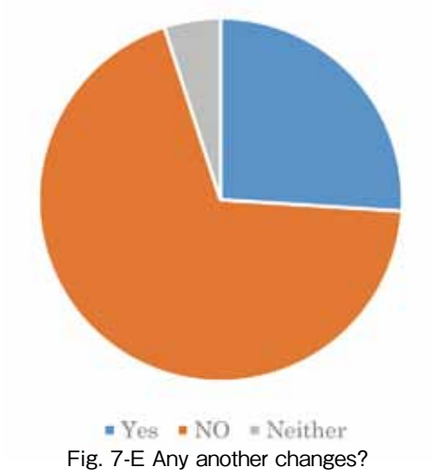

Fig. 7-E Any another changes?

Three 'Yes' were seen. Two patients answered "my condition became better". The other answer was "I was glad to improve my laboratory data".

f) Questionnaire Sheet (Fig. 7)

1) Could you take the tablet of Polaprezinc easily?
Twenty-five% of patients answered yes. pharyngeal incongruity(one case), difficulty in taking the tablet due to disabled hands.

2) Does your wound was healed fast?
Twenty-four % of patients answered yes, 52% patients answered No,24% patients were neither.

3) Does your taste was improved?
Fourteen % of patients answered yes. 86% of patients answered No.

4) Does your appetite was improved?
Fifteen % of patients answered yes, 80% patients answered No,5% patients were neither.

5) If you feel another change in your feeling after taking the tablet, please write. There were three opinions. The first was 'my condition became well'. The second was 'I was glad to see improvement in my laboratory data'. The third was 'I became very fine!'

Discussion

The Japanese Society for Dialysis Therapy recommends that the anemia management in CKD patients especially in hemodialysis patients should be generally treated by rhEPO or iron therapy into target range 10 to 12 g/dl of hemoglobin[7]. However, there is still an urgent need of elucidating the etiology of refractory anemia with no response to ESA. At the same time, it is anticipated that treatments for anemia in CKD patients, in addition to ESA and iron products, will emerge[8]. We planned the present study based on result indicating that dialysis patients have significantly decreased serum zinc concentration[4,5], and the disease concept of the Zinc Deficiency Anemia(ZDA)[9]. In this study, our results about the changes of serum zinc concentration and anemia level were similar to previous study[3]. Polaprezinc could elevate their zinc level into normal range, and also improve their anemia level. With regard to anemia, their hemoglobin level was not changed, however, the necessary dosage of DA to keep their hemoglobin level in 10 to 12 g/dl was reduced 7.2μg/week. This amount of ESA is very little, but it's very expensive. In Japanese medical situation, the cost for hemodialysis session includes all kinds of medicines or necessary devices, for example ESA, iron agent, some prescribed medicine, dialyzer or dialysate. As you may know, the lower costs make the higher benefit so called money gain. The cost of DA is 1μg=240 Yen(approx. 2US$). Based on these exchange and calculation, we have 18 patients with zinc supplementation, therefore 18*240Yen/week=17280Yen(144US$)/month could be saved. Surprisingly, 207360 Yen(1728 US$)can be saved overall.

Recently, the effectiveness of zinc supplementation therapy has been reported. In Japanese medical scene, especially in hemodialysis field the zinc supplementation therapy has been recognizing one of the effect therapy in general. On the other hand, copper deficiency anemia has been reported[6]. Although The mechanism of copper deficiency has not been clarified, Kanbe pointed out that copper absorption is inhibited by saturated status of zinc based on the theory of Irving-Williams series[10,11]. In this study, the patient's serum copper level was not changed after zinc supplementation. All patients are in outpatient. They can take a usual diet in their home, and they are in good nutrition status. In this nutritional condition, 34mg of daily zinc supplementation can be caused a risk of copper

deficiency.

In this study, we carried out a questionnaire about taking Polaprezinc tablet. Polaprezinc is originally an anti-gastric ulcer agent commercial name is Promac®(ZERIA Pharmaceutical Co Ltd, Tokyo). In Japan, the zinc including anti-gastric ulcer agent is generally used. Polaprezinc can supply 34mg of zinc per day quantitatively, and easy to take as a tablet, on the other hand, other zinc supplying agent as zinc sulfate hydrate is too stinking to take.

In our questionnaire only one case complained pharyngeal incongruity, it presents the easiness in taking this tablet. Also, major side effect was not seen during zinc supplementation. Questionnaire also disclosed improvement of their general condition. Regarding with taste, wound healing and appetite, there is few patients answered as improving. There is no patient who complained any complications or replied as exacerbation. Therefore zinc supplementation might be done safety. Moreover, some patients who were taking Polaprezinc in this study felt improving their general condition. The zinc supplementation by Polaprezinc is effective, without severe complication. Therefore patients undergoing hemodialysis should be recommended to measure serum zinc level and in case of lower zinc level, zinc supplementation might be considered.

◆ References

1）Iseki K：Screening for renal disease, what can be learned from the Okinawa experience. Nephrol Dial Tranplant 18：899-905, 2003

2）Silverberg D, Dov Wexler 2, Blum M, Wallman Y, Iaina A：The cardio–renal anaemia syndrome：does it exist? Nephrol Dial Tranplant 18（Supple）viii7-12, 2003

3）Fukushima T, Horike H, Fujiki S, Kitada S, Sasaki T, Kashihara N：Zinc deficiency anemia and effects of zinc therapy in maintenance hemodialysis patients. Ther Apher Dial 13：213-219. 2009

4）Zumkley H, Bertram HP, Lison A, Knoll O, Losse H：Aluminum, zinc and copper concentrations in plasma in chronic renal insufficiency. Clin Nephrol 12：18-21, 1979

5）Hosokawa S, Yoshida O：Effect of erythropoietin（rHuEpo）on trace elements and quality of life（Qol）in chronic hemodialysis patients. Int J Clin Pharmacol Ther, v. 32, n. 8, p415-421, 1994.

6）Rowin J, Lewis Sl：Copper deficiency myeloneuropathy and pancytopenia secondary to overuse of zinc supplementation. J Neurol Neurosurg Psychiatry 76：750-751, 2005

7）2015 JSDT Guideline for Renal Anemia in Chronic Kidney Disease 49(2)：89-158, 2016（Language in Japanese）

8）Go AS, et al：Chronic Kidney Disease and the risk of death, cardiovascular event and hospitalization. New Engl J Med 351：1296-1305, 2004

9）Plasad A, et al：Syndrome of iron deficiency anemia, hepatosplenomegary, dwarfism and geophagia. Am J Med 313 532-546, 1961

10）Irving H M N H, Williams R J P：The stability of transition-metal complexes. J Chem Soc：3192–3210. 1953

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