Effect of Pharmacist Management on Serum Hemoglobin Levels with Renal Anemia in Hemodialysis Outpatients

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Regulatory Article

The initiation of a pharmacist-implemented management program to ensure appropriate use of erythropoietin-stimulating agents at Mizushima Kyodo Hospital is described. In the present study, we examined the influence of having pharmacists actively manage hemoglobin levels on therapeutic outcome in a retrospective study of 84 outpatients receiving hemodialysis. We compiled in-hospital guidelines for the use of erythropoietin and iron for outpatients with renal anemia. Pharmacists made recommendations, particularly about changes in the dose of erythropoietin and administration of iron preparations, to physicians. Clinical test results were monitored for 12 months (between November 2007 and October 2008) with and without the participation of pharmacists (continuous 6 months). The counseling by pharmacists significantly decreased hemoglobin levels in the high group (>12 g/dl) and significantly increased them in low group (<10 g/dl). Furthermore, it increased hemoglobin levels in the optimal group, suggesting the management of our hospital guidelines. On the other hand, low levels of hemoglobin indicated low levels of albumin. It is suggested that no improvement in hemoglobin levels may indicate low levels of albumin. These findings suggest that the active participation of pharmacists in the management of renal anemia in hemodialysis patients had a great therapeutic impact.

Key words: renal anemia; hemodialysis; erythropoietin; hemoglobin; pharmacist

It is hoped that the clinical activities of pharmacists will enhance the quality of drug therapy. The anemia of chronic renal failure is usually characterized as a normocytic, normochromic form occurring in end-stage renal disease. Renal anemia is a major complication in hemodialysis patients. The primary cause in patients with end-stage renal disease is insufficient production of erythropoietin by the kidneys. Currently, recombinant human erythropoietin is the standard treatment for renal anemia in end-stage renal disease patients and has been shown to improve quality of life and improve cardiac function. Furthermore, managing renal anemia with erythropoietin and iron replacement in hemodialysis patients poses several clinical challenges, including the maintenance of stable hemoglobin levels within narrow target ranges, balancing iron and erythropoietin dosages, and optimizing the response to erythropoietin to achieve the lowest possible effective erythropoietin dose. In recognition of this situation, clinical guidelines such as the “2008 guidelines for renal anemia in chronic kidney disease by the Japanese society for dialysis therapy,” with recommended targets for hemoglobin (10—11 g/dl) and iron indices (transferring saturations (TSAT) <20%, ferritin <100 ng/ml), require ongoing updates as the optimal management strategy for renal anemia in hemodialysis patients has yet to be fully delineated. Furthermore, effective and efficient means of implementing these strategies into clinical practice have yet to be explored. The active participation of pharmacists in erythropoietin and iron replacement therapy for renal anemia in hemodialysis patients is recommended.

In Mizushima Kyodo Hospital (Kurashiki, Okayama, Japan), pharmacists have been part of a hemodialysis care team, and active participants in the treatment of hemodialysis patients since April 2008. Before that time, only physicians were responsible for checking blood parameters, and deciding dosages of erythropoietin and iron. In addition, each doctor had to make decisions for hemodialysis patients without pharmacists’ suggestions. In the present study, we decided on hospital guidelines for the use of erythropoietin and iron to help unify pharmacists’ suggestions to physicians for erythropoietin and iron replacement therapy. Furthermore, to explore the role of the pharmacists’ participation, we examined the influence of hemoglobin levels anteroposterior the participation.

MATERIALS AND METHODS

Outline of the Outpatient Hemodialysis Unit in Mizushima Kyodo Hospital in Japan Six physicians and three pharmacists work regularly in the outpatient hemodialysis unit (35 beds with a hemodialysis apparatus) in Mizushima Kyodo Hospital (282 beds). There were 84 hemodialysis patients (48 males and 36 females; average age of 62 years; average hemodialysis duration of 8.6 years) as of April 2008. A pharmaceutical care service including patient education and medication by pharmacists started for all hemodialysis outpatients from April 2008.

Ten pharmacists work regularly in our hospital, and all of them participated in pharmaceutical care including patient education. Three pharmacists were responsible for the pharmaceutical care of hemodialysis outpatients, and provided education and related pharmaceutical services to each patient.
at least once a month. The work load for pharmacists was well organized, and not excessive.

**Pharmacists’ Clinical Activities for Hemodialysis Outpatients** Pharmacists performed clinical management including five main activities 1) providing drug information on renal anemia to physicians; 2) compiling guidelines for proper use of recombinant human erythropoietin and iron in collaboration with physicians; 3) medication use evaluations based on laboratory data; 4) proposing plans to change prescriptions based on medication use evaluations and 5) providing drug information and lifestyle care point to patients.

**Monitoring of Therapeutic Effects of Pharmacists’ Activities** The present pharmacist-implemented program was adopted at our hospital from April 2008. In the present study, the laboratory data were collected between November 2007 and October 2008: a retrospective study of 84 patients on hemodialysis in our hospital. The patients were categorized into three groups based on hemoglobin levels, low (<10 g/dl), optimal (10—12 g/dl) and high (>12 g/dl), in November 2007 (before the pharmacists’ participation) or April 2008 (pharmacists’ participation had started), respectively. All experiments were conducted according to the ethics committee of Mizushima Kyodo Hospital.

**Statistics** All values are expressed as the mean ± S.D. of a group. The data was assessed using either a one-way analysis of variance (ANOVA) or Student’s t-test. The group means were compared using Dunnett’s test for multiple comparisons. Categorical variables of patients on hemoglobin levels were compared using χ² test. Statistical significance was based on a probability value of less than 0.05.

**RESULTS**

**Hospital Guidelines for the Use of Erythropoietin** All patients on hemodialysis received erythropoietin for renal anemia in November 2007. As a result of discussions with physicians, three therapeutic targets, hemoglobin levels, TSAT, and ferritin, were employed. Then we referred to the Japanese society for dialysis therapy. Recombinant human erythropoietin (epoetin beta) was administered 3 times weekly, and darbepoetin alfa, once weekly. By checking hemoglobin levels, pharmacists made recommendations to physicians to change the dose of erythropoietin. For low responders, pharmacists checked ferritin and TSAT levels, and made recommendations to give an iron preparation (ferric oxide, saccharated for intravenously (i.v.) administration; sodium ferrous citrate for oral administration) when iron deficiency was evident. The iron preparation at 40 mg was administered i.v. once a week to patients with ferritin and TSAT values of less than 60 ng/ml and 20%, respectively. In one exceptional case, a patient who had a history of allergic reaction to i.v. iron preparations received an oral iron preparation at 100—200 mg once a day. Detailed guidelines are shown in Fig. 1. The original proposal for the guidelines was made by pharmacists, and then improved through discussion with physicians.

**Therapeutic Outcome of the Pharmacist-Implemented Management Program** Figure 2 illustrates the time-dependent change in hemoglobin levels in all patients from November 2007 to October 2008. In the optimal level group, hemoglobin levels were maintained. Hemoglobin levels were significantly increased in the low level group from an early stage. However, those of the high level group improved in the late stage. Figure 3A illustrates the time-dependent change in hemoglobin levels without the pharmacist-implemented management program from November 2007 to March 2008. Hemoglobin levels were significantly increased in the low level group, but unaffected in the high and optimal level groups. Figure 3B illustrates the time-dependent change in hemoglobin levels over the duration of the pharmacist-implemented management program from April 2008 to October 2008. Hemoglobin levels were significantly increased in the low level group and decreased in the high level group. Tables 1 and 2 show the change in the number of patients in the three groups without and with the pharmacist-implemented management program. There was no effect of categorical variables of patients on hemoglobin levels without the program (χ² = 5.12, p = 0.07; Table 1). However, there was a signifi-
Pharmacist management | Low | Optimal | High | $\chi^2$ | $p$-value
---|---|---|---|---|---
No (Nov. 2007) | 38 | 40 | 6 | 5.12 | 0.07
Yes (Apr. 2008) | 26 | 45 | 13 | | |

Hemoglobin levels are given as low (<10 g/dl), optimal (10—12 g/dl) and high (>12 g/dl). Categorical variables were compared using $\chi^2$ test.

Table 2. Changes in the Number of Hemodialysis Patients with Low, Optimal and High Levels of Hemoglobin with and without the Pharmacist Management Program at Start-up

Pharmacist management | Low | Optimal | High | $\chi^2$ | $p$-value
---|---|---|---|---|---
No (Mar. 2008) | 23 | 46 | 15 | 6.86 | 0.03
Yes (Oct. 2008) | 17 | 61 | 6 | | |

Hemoglobin levels are given as low (<10 g/dl), optimal (10—12 g/dl) and high (>12 g/dl). Categorical variables were compared using $\chi^2$ test.

DISCUSSION

Clinical guidelines derived from evidence-based medicine assist physicians in decision-making that benefits patient care. Translating practical guidelines into dosing protocols that can be implemented by members of hemodialysis care teams with pharmacists should yield similar beneficial outcomes. Renal anemia management protocol development and implementation by pharmacists, nurses and multidisciplinary groups for hemodialysis patients have been reported. In Japan, clinical practice guidelines such as the “2008 guidelines for renal anemia in chronic kidney disease by the Japanese society for dialysis therapy,” have been suggested.9) This protocol recommended hemoglobin levels of 10—12 g/dl. Furthermore, above 12 g/dl of hemoglobin, it recommended a reduction in dose or withdrawal of erythropoietin. On the other hand, the iron replacement therapy of this protocol started with less than 20% of TSAT or 100 ng/dl of ferritin. In our hospital, pharmacists have been part of the hemodialysis care team with physicians and nurses since April 2008. As a result of discussions with physicians, three therapeutic targets, hemoglobin levels, TSAT and ferritin levels, were employed. TSAT percentage and ferritin levels are standard parameters of iron storage that practitioners routinely measure to guide anemia management in hemodialysis pa-

Fig. 3. Changes in Hemoglobin Levels on the Active Participation of Pharmacists in the Management of Renal Anemia with Hemodialysis Outpatients

(A) Time-dependent change in hemoglobin levels without the pharmacist-implemented program of managing hemodialysis outpatients from November 2007 to March 2008. (B) Time-dependent change in hemoglobin levels with the pharmacist-implemented program from April 2008 to October 2008. The low level group has hemoglobin levels of <10 g/dl. The optimal level group has hemoglobin levels of 10—12 g/dl. The high level group has hemoglobin levels of >12 g/dl. Values are expressed as the mean±S.D. Data were analyzed with a one-way analysis of variance (ANOVA) and group means were compared using Dunnett’s test for multiple comparisons. (A) * $p$ < 0.05, ** $p$ < 0.01, significantly different from November 2007. (B) * $p$ < 0.05, ** $p$ < 0.01, significantly different from April 2008.

Table 1. Changes in the Number of Hemodialysis Patients with Low, Optimal and High Levels of Hemoglobin with and without the Pharmacist Management Program at Start-up

Fig. 4. Differences in Albumin Levels with Low and Optimal Levels of Hemoglobin in Hemodialysis Outpatients

We examined albumin levels in October 2008 among hemodialysis outpatients. The low level group and optimal level group had hemoglobin levels of <10 g/dl and 10—12 g/dl respectively, in October 2008. Values are expressed as the mean±S.D. The group means were compared using Student’s $t$-test. * $p$ < 0.05, significantly different from the optimal group.

Fig. 5. Changes in Hemoglobin Levels Based on Albumin Levels in Hemodialysis Outpatients

We examined albumin levels in November 2007 among hemodialysis outpatients. The low level group and other group had hemoglobin levels below or above 3.3 g/dl, respectively. Values are expressed as the mean±S.D. The group means were compared using Student’s $t$-test. * $p$ < 0.05, ** $p$ < 0.01, significantly different from November 2007.

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tients. However, iron storage levels may increase the risk of bacteremia among hemodialysis patients starting intravenous iron therapy. Furthermore, repeated intravenous administration of iron to hemodialysis patients was associated with signs of increased oxidative DNA injury, as reflected by increased serum levels of 8-hydroxy-2'-deoxyguanosine. As these changes were accompanied by increased serum ferritin levels, excess body iron stores might play an important role in oxidative stress. Namely, one must carefully monitor the hyperiron situation. We decided on iron replacement therapy starting with less than 20% of TSAT or 60 ng/dl of ferritin in our hospital.

Allen et al. reported that assessments of a pharmacist’s educational program for hemodialysis patients seem to lead to optimal hemoglobin levels within 2 months. Furthermore, the active participation of pharmacists in the management of renal anemia in hemodialysis patients increased the number of patients with hematocrit levels above 30% of the therapeutic target. In this study, pharmacists were responsible for checking blood parameters, deciding the dosage of erythropoietin. Without the pharmacist management program, hemoglobin levels were significantly increased in the low level group. However, there was no effect in the high level group. Furthermore, there was no effect of categorical variables on hemoglobin levels without the pharmacist management program. On the other hand, there was a significant effect of categorical variables with the pharmacist management program. In particular, there was a significant decrease in hemoglobin levels in the high level group. Singh et al. reported the use of a target hemoglobin level of 13.5 g/dl (as compared with 11.3 g/dl) to be associated with an increased risk (e.g. congestive heart failure, myocardial infarction, serious adverse event) among patients with anemia caused by chronic kidney disease. Furthermore, no incremental improvement in the quality of life was observed.

Hence, this report recommended the use of a target hemoglobin level of 11.0 to 12.0 g/dl rather than a level of 11.0 to 13.0 g/dl. Namely, the active participation of pharmacists greatly improved hemoglobin levels in hemodialysis patients, particularly the high level group. The present study should be considered a pilot study. The impact of such active participation of pharmacists has to be confirmed with a large sample.

In general, malnutrition is recognized in hemodialysis patients. It was reported that hypoalbuminemia is an important predictor of mortality in hemodialysis patients. Between 23 and 76% of hemodialysis patients are reported to be malnourished. In this study, we examined the effect of erythropoietin treatment on albumin levels based on the relationship between low and optimal levels of hemoglobin in October 2008. The low levels of hemoglobin significantly decreased albumin levels. Furthermore, the group with low levels of albumin had significantly decreased hemoglobin levels compared to the group with more than 3.3 g/dl of albumin. These findings suggest that the low responders to erythropoietin may have low levels of albumin. Namely, it may be necessary to maintain albumin levels to improve the renal anemia in hemodialysis patients. Furthermore, studies are in progress to clarify complications with hepatitis.

In conclusion, pharmacist-implemented management of pharmaceutical care of the patients contributed to an improvement in renal anemia in hemodialysis patients.

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REFERENCES