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Clinical efficacy of two forms of intravenous iron—saccharated ferric oxide and cideferron—for iron deficiency anemia

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Over 90% of iron deficiency anemia cases are due to iron deficiency associated with depletion of stored iron or inadequate intake. Parenteral iron supplementation is an important part of the management of anemia, and some kinds of intravenous iron are used. However, few studies have evaluated the clinical efficacy of these drugs. The purpose of this study was to compare and assess the clinical efficacy of two types of intravenous iron injection, saccharated ferric oxide (SFO) and cideferron (CF). Medical records were obtained for 91 unrelated Japanese anemia patients treated with SFO (n = 37) or CF (n = 54) from May 2005 to May 2010 at Gunma University Hospital. Patients treated with blood transfusion, erythropoietin or oral iron were excluded. Hemoglobin (Hb) values measured on day 0, 7 and 14 were used to assess the efficacy of intravenous irons. A significant increase was observed in the mean Hb value by day 14 of administration in both the CF group and SFO group, and the mean Hb increase due to administration of CF for 7 days was comparable to that of SFO for 14 days. Age and sex did not affect improvement of Hb value. CF is fast acting and highly effective compared with SFO for the treatment of iron deficiency anemia. The use of CF may shorten a therapeutic period for iron deficiency anemia, and CF may be feasible for reducing the hospitalization period.

1. Introduction

Iron deficiency anemia (IDA) and sideropenia are frequent symptoms in the general population and present particularly often in patients with chronic diseases such as inflammatory bowel disease, rheumatoid arthritis, chronic kidney disease, chronic heart failure, and cancer. Over 90% of IDA cases are due to iron deficiency associated with depletion of stored iron or inadequate intake (Bashiri et al. 2003). Iron deficiency is an important cause of anemia, which in turn can trigger hospitalization and even mortality. Anemia leads to an increased length of hospitalization and increased risks such as transmission of infectious diseases due to blood transfusion (Dickason et al. 1992; Scholl 2005). Recently, the efficacy of oral iron replacements has been questioned, because gastrointestinal iron absorption has limits and thus may not be able to balance continuous iron loss (Schreiber et al. 1996). In addition, an elevated hepcidin level has been reported to inhibit enterocytic iron transport through internalization of ferroportin (Nemeth et al. 2004). A shortage of iron can be aggravated by chronic blood loss leading to absolute iron deficiency and IDA. Thus, management of iron deficiency through addressing iron availability and iron stores has been suggested as a critical issue. Improvement of hemoglobin (Hb) values in anemia patients can be achieved by systemic iron treatment and is associated with improved quality of life, independently of changes in disease activity (Wells et al. 2006). Because of risks of infection, increased oxidative stress and worsening of viral hepatitis by intravenous iron, intravenous iron drugs are used only for patients who cannot take oral iron drugs such as tetrasodium biscitrato iron (II), ferrous sulfate, ferrous fumarate and ferric pyrophosphate or for patients who need immediate supplementation of iron; however, intravenous iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron (Kulnigg et al. 2008; Lindgren et al. 2009). Thus, recently, parenteral iron supplementation has been regarded as an important part of the management of anemia (Bodemar et al. 2004; Gasche et al. 2001; Schröder et al. 2005). Recently, two kinds of intravenous iron, saccharated ferric oxide (SFO) and cideferron (CF), have been used in Japan mainly for the treatment of anemia caused by iron deficiency.

SFO is also known as iron sucrose and is used worldwide. The particular size of SFO is sufficiently small to pass through the glomerular basement membrane. On the other hand, CF is a macromolecular complex of ferric hydroxide complexed with dextrin and citric acid, and it is unfilterable by the glomerular basement membrane. This structure has good physicochemical stability and reduces the generation of iron radicals. Due to these differences, CF is expected to be taken up by reticuloendothelial cells smoothly and to produce Hb quickly while reducing the increase of oxidant stress caused by iron radicals.

However, there are few reports on the clinical efficacy of these drugs. The purpose of this study was to compare and assess the clinical efficacy of the two intravenous iron injections, SFO and CF. To the best of our knowledge, this is the first report comparing the clinical effects on improvement of Hb values by SFO and CF.

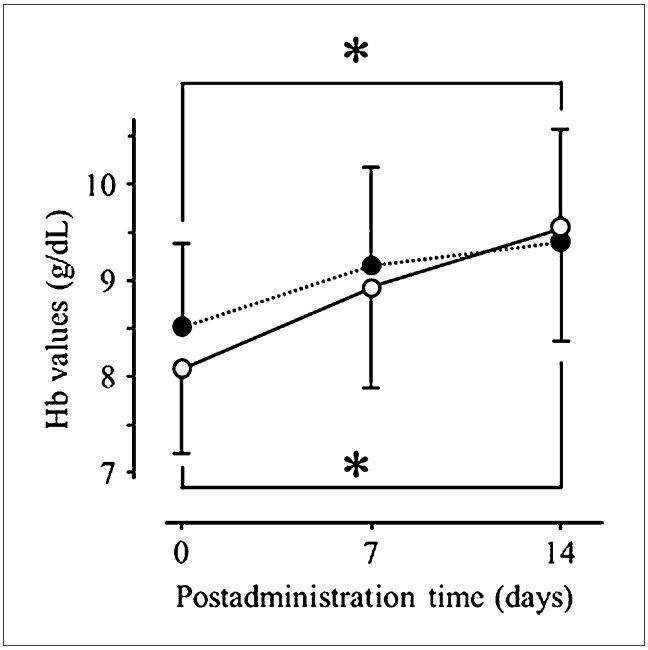

Fig. 1: Change of Hb values. Symbols and vertical bar represent the mean ± S.D. Open circle: CF ($n = 54$); closed circle: SFO ($n = 37$); *: $p < 0.05$

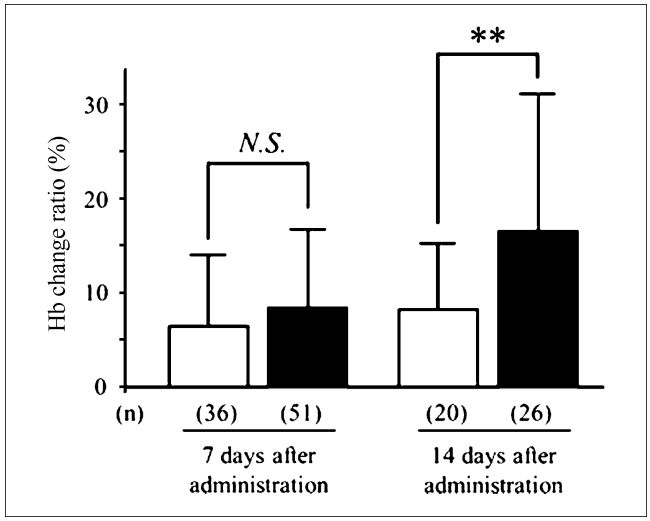

Fig. 2: Treatment with intravenous iron, and Hb change ratio. Symbols and vertical bars represent the mean ± S.D. Open bars: SFO; closed bars: CF; **: $p < 0.01$

2. Investigations and results

2.1. Patient characteristics

The percentage of males and the mean age of the SFO group were 62.2% and 61.6 ± 16.6 years old, respectively, and those of the CF group were 59.3% and 56.4 ± 22.7 years old, respectively. Hb values at the onset of treatment with SFO and CF were 8.48 ± 0.88 and 8.04 ± 0.97 g/dL, respectively. The average total dose of administration of SFO and CF was 1.65 ± 0.54 and 1.52 ± 0.49 ampules/day, respectively.

2.2. Iron administration and change of hemoglobin value

The mean Hb value on day 14 of administration in both the CF group and SFO group was higher than that at the beginning of treatment (Fig. 1). The increased ratio of Hb at 7 and 14 days treatment in the CF group (8.5 ± 8.4% and 17.8 ± 14.3%, respectively) was significantly higher than that of the SFO group (6.4 ± 7.6% and 7.8 ± 6.8%, respectively) ($p < 0.05$), and the mean Hb increase following administration of CF for 7 days was comparable to that of SFO at 14 days (Fig. 2).

2.3. Impact of age and sex on the effect of iron administration treatment

Fig. 3 shows the relationship between age and the effect of 14 days of treatment. No significant correlation between age and Hb change ratio following treatment with CF or SFO was found. Fig. 4 shows the relationship between sex and the effect of treatment. In this study, a significant difference in the Hb change ratio after 14 days of administration between the CF group and SFO group was found only in males. Although females showed the same tendency as the males, it did not reach statistical significance. No influence of sex on the clinical efficacy of CF or SFO was found.

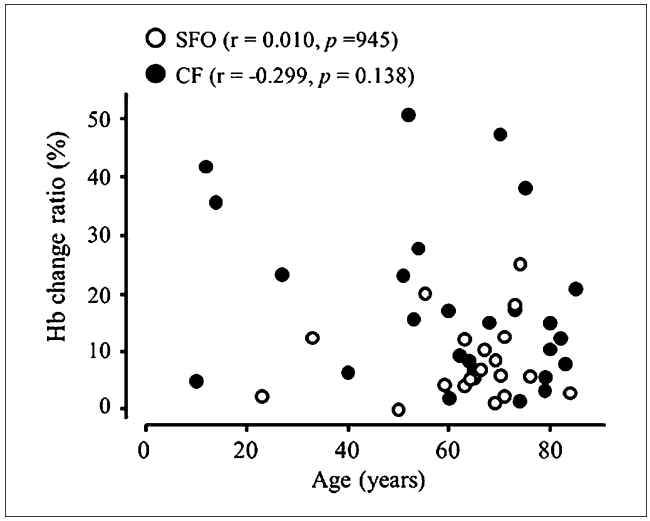

Fig. 3: Relationship between age and the Hb change ratio after 14 days of treatment with intravenous iron. Open circle: SFO ($n = 20$, r = 0.010, $p = 0.945$); closed circle: CF ($n = 26$, r = -0.299, $p = 0.138$); *: $p < 0.05$

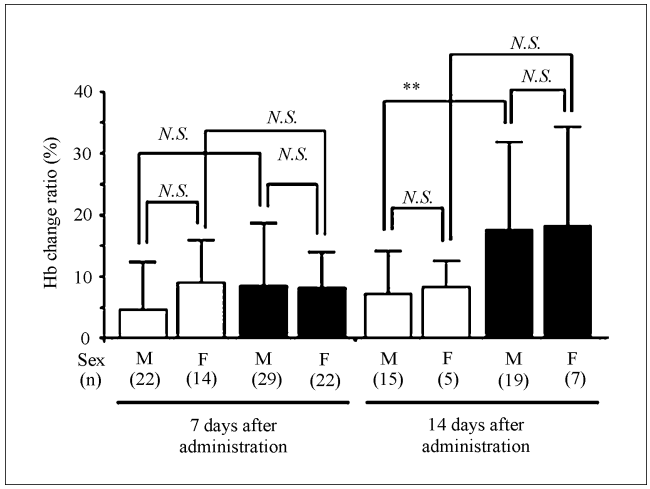

Fig. 4: Influence of sex on the clinical effect of intravenous iron administration. Symbols and vertical bars represent the mean ± S.D. Open bars: SFO; closed bars: CF; **: $p < 0.01$

3. Discussion

We compared and assessed the clinical efficacy of two types of intravenous iron injection, SFO and CF. Our data showed

that CF was more effective than SFO, and the effect of 7 days of treatment with CF was similar to that of 14 days of treatment with SFO. This suggested that CF can shorten the therapeutic period for IDA and reduce the hospitalization period. This difference of therapeutic effect might be due to the difference of iron uptake kinetics. CF consists of a macromolecular complex of ferric hydroxide with dextrin and citric and is not filterable by the glomerular basement membrane, while SFO is filterable because of its small particle size.

We also assessed the influence of sex and age on the efficacy of iron injection. In males, a significant difference in mean Hb increase was found. On the other hand, although CF was more effective than SFO in females, the difference did not reach statistical significance, possibly because of the small sample size provided. Data of females showed the same tendency as that of males. We also could not find a significant correlation between age and the Hb change ratio following treatment with CF or SFO. Thus, we confirmed that, from the view point of improvement of Hb value, CF was significantly more effective compared with SFO and might shorten the therapeutic period of IDA, regardless of age or sex. Although we clarified the difference in the clinical efficacy between intravenous iron drugs, we could not assess the influence of medical condition or severity of disease in patients due to the small sample size. There are some alternative possible factors such as difference of distribution of iron in bone marrow or availability; however, we could not assess the detailed kinetics of iron metabolism. In the future, to clarify this point, we should analyze the disposition of iron components such as ferritin or transferrin. We should also establish the difference of pharmacokinetics of components containing iron, such as ferritin or transferrin, between the use of CF and SFO, as well as the contribution of PK difference on clinical efficacy.

In conclusion, cideferron is fast acting and highly effective compared with saccharated ferric oxide for the treatment of deficiency anemia. The use of cideferron may shorten the therapeutic period for IDA, and CF may be feasible for reducing the hospitalization period.

4. Experimental

4.1. Subjects

Ninety-one unrelated Japanese anemia patients treated with SFO (n = 37) or CF (n = 54) from May 2005 to December 2010 at Gunma University Hospital were enrolled. The Hb value as a primary end point and other inpatient data were collected retrospectively from patient medical records.

Patients treated with blood transfusion or oral iron before or after 14 days of administration of intravenous iron were excluded. Patients treated with erythropoietin for 1 month before or after administration of intravenous iron and those with an Hb value over 10 g/dL at the onset of treatment were excluded. Furthermore, patients receiving presurgical iron injections for autologous blood transfusion or patients with overt hemorrhage were excluded. This study was approved by the Gunma University Hospital Institutional Review Board.

4.2. Statistical analysis

The chi square test, Mann-Whitney's U-test and the Kruskal-Wallis test were conducted in SPSS ver. 19.0. Results are presented as mean ± S.D. A P value of less than 0.05 was considered statistically significant. Because of the difference of iron content in one ampule (SFO contains 40 mg of Fe and CF contains 50 mg of Fe per ampule), the mean change of Hb was adjusted for therapeutic periods and iron requirements.

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