

Clinical effect of *Caulis* decoction on iron deficiency anemia and the hepcidin iron metabolism

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Abstract: Studies have shown that Chinese herb caulis extract can effectively inhibit the expression of the core regulatory hormone hepcidin in iron metabolism and significantly increase the iron level in the body. On this basis, this paper analyzed clinical efficacy and safety of oral niferex (polysaccharide iron complex) combined with caulis Decoction in the treatment of iron deficiency anemia. The results showed that the recovery rate of the Caulis group, Niferex group and the combined treatment group were 41.6%, 46.6% and 58.3% respectively. The difference of recovery rate was statistically significant. The RBC, Hb, Hct, SI, SF, Tf, TIBC and serum Heparin in the combined treatment group were significantly higher than those in the other groups ($P < 0.05$). Caulis group has 3 cases of gastrointestinal symptoms, and the incidence of adverse reactions was 5%. Chinese medicine caulis can significantly improve erythrocyte count, hemoglobin, hematocrit and related iron metabolism, but the improvement of the combined treatment group is more obvious. In conclusion, Chinese medicine caulis can significantly improves the clinical symptoms and iron metabolism in patients with iron deficiency anemia, combined oral niferex therapy has better effect.

Keywords: Iron deficiency anemia, caulis, regulatory hormone, gastrointestinal symptoms, herbal extracts.

INTRODUCTION

Iron deficiency anemia (IDA) refers to the imbalance of iron supply and demand in the human body, which leads to the gradual depletion of iron elements stored in the body, and then anemia caused by the lack of iron content in the red cells (Okuyama *et al.*, 2015). According to the WHO report, there are about 2 billion 150 million people around the world suffering from iron deficiency of varying degrees (Szewczyk *et al.*, 2015). Because iron deficiency leads to the decrease of the activity of many enzymes and the influence of cell metabolism, the immune function, behavior and development of the body, gastrointestinal tract, skin mucosa, and nervous system have some blood system performance (Park *et al.*, 2015). At present, the treatment is mainly using inorganic iron sulphate and organic iron complex, but it is easy to produce a series of side effects, such as constipation, diarrhea and weight loss and the use of a variety of iron fortified food, such as iron soy sauce, fortified iron soybean milk and rice flour, not only potentially have the above adverse reactions (Rosenthal *et al.*, 2015). The absorption and utilization of inorganic iron is also low. Caulis is a commonly used Chinese herbal medicine. It has been found that *Caulis* plays an important role in regulating iron metabolism and improving anemia in rats with iron deficiency anemia. On this basis, the clinical efficacy and safety of oral niferex (Polysaccharide Iron Complex) combined with caulis decoction in the

treatment of iron deficiency anemia were studied in this study (Simone *et al.*, 2016).

After entering the twenty-first Century, scientists had long searched for the nuclear molecules that regulate iron metabolism, and the 25 amino acids of the liver secreted by the hormone hepcidin were found (Udali *et al.*, 2015). Heparin reduces the absorption of iron in the small intestine and the iron recovery of macrophages by interacting with the iron pump protein ferroportin distributed on the small intestine and giant cells, thus maintaining the homeostasis of iron in the body (Muraki *et al.*, 1985; Zhu *et al.*, 2015). Genetic mutations or acquired hepcidin disorders lead to iron deficiency or iron overload. Heparin can feedback iron content and hematopoietic iron demand. In mouse models, hepcidin mRNA was upregulated in mice fed high iron and was downregulated in hypoxia and anaemia (Wu *et al.*, 2013). As for the detection of hepcidin in human blood, there is no very effective antibody at present, so it is estimated that the concentration of hepcidin in urine is used. When the body was in the state of iron deficiency and inflammation, hepcidin decreased, while hepcidin was positively correlated with the level of ferritin in serum.

The extract of Chinese herbal medicine used in traditional Chinese medicine which can effectively inhibit the expression of the core regulating hormone Heparin and improve the iron level of the body (Schneider *et al.*, 2011). It was found that the extract of 16 kinds of traditional

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Chinese medicine used in traditional Chinese medicine on the expression of hepcidin was found to reduce the expression of hepcidin mRNA, and further cell experiments confirmed that the inhibitory effect of the Caulis to hepcidin was achieved by reducing the phosphorylation of protein Smad1/5/8 (Yoshio *et al.*, 2013). After adding the extract from Caulis to feed, the expression of hepcidin mRNA in liver tissue of mice was decreased, and the serum iron level increased significantly. These results suggest that Caulis decoction can effectively improve the body iron status and have certain preventive and therapeutic effects on iron deficiency anemia.

MATERIALS AND METHODS

Clinical data

180 cases of iron deficiency anemia were selected from January 2016 to September 2017 in our hospital. All patients were in accordance with the standard of diagnosis and curative effect of blood diseases formulated by the national hematological academic conference. Inclusion criteria: Western medicine diagnostic criteria for iron deficiency anemia; age less than 75 years old; volunteers as subjects, who have signed informed consent. Exclusion criteria: (1) Age > 75 years old; (2) Patients with serious heart, liver, kidney disease and dysfunction; (3) Pregnancy, lactation and psychotic patients; (4) The history of drug and food allergies; (5) Does not conform to the inclusion criteria. All patients showed signs of palpitation, shortness of breath, dizziness, tinnitus and other anemic symptoms after exercise.

According to the random number method, 180 cases were divided into 3 groups: Chinese medicine caulis, niferex (iron polysaccharide complex capsules) group, and combined treatment group. There were 60 cases of Caulis, 38 males and 22 females, aged 15~74 years, with an average of (43.15±7.26) years. There were 60 cases in niferex group, 33 cases of male and 27 cases of female, and the average age was 15~73 years old (42.28 ±7.59) years. The combined treatment group consisted of 60 patients, 35 males and 25 females, aged 13~73 years, with an average age of (41.59 ± 7.80) years. The two groups of age, sex, and other clinical data, the difference was not statistically significant (P>0.05), comparable, and the study was approved by the ethics committee of our hospital, and the batch number was YYDH15-6.

Methods

Caulis decoction was given 15 g/day and 42 days continuously. 15g indicated that the decoction contained 15g dry weight of caulis. Niferex group can be treated with niferex capsule, oral orally can be 150 mg/d. The combined treatment group was given 15g /day of water extract of caulis and niferex capsule 150 mg, 1 time every day.

Observation index

The clinical efficacy, blood related indexes and incidence of adverse reactions before and after treatment were compared between the two groups. The standard of evaluation of curative effect: the bad signs and clinical symptoms basically disappeared, the female serum protein >110 g/L, the male serum protein >120 g/L were cured, the clinical signs and symptoms were significantly improved, and the level of anemia was improved to the II level. Clinical signs and symptoms improved, anemia improved I level and no improvement in clinical signs, symptoms and anaemia was ineffective; total effective = (cure + significant + effective) / total number * 100%. At the same time, the score of TCM clinical symptoms of patients was scored, with a score of 0-4 points. The higher the score means the more serious the symptoms.

STATISTICAL ANALYSIS

SPSS 19 software analysis the data, $\bar{x} \pm s$ to express measurement data, normal distribution and variance of the two independent samples of the average number of samples using t test, n (%) to represent the count data, the inter group distribution using χ^2 test, P<0.05 indicates that the difference is statistically significant.

RESULTS

Comparison of clinical efficacy

After 42 days treatment, the cure rates of caulis group, niferex group and combined treatment group were 41.6%, 46.6% and 58.3% respectively. The difference of cure rate between the groups was statistically significant ($\chi^2=7.451$, P<0.05). There was no significant difference in the cure rate between Caulis group and iron group ($\chi^2= 0.846$, P>0.05). The cure rate of combined treatment group was significantly higher than that of Chinese medicine Caulis group and niferex group ($\chi^2= 5.247, 3.265$, P<0.05), as show in table 1.

Comparison of experimental indexes

There was no significant difference in erythrocyte count (RBC), hemoglobin (Hb), hematocrit (Hct), serum iron (SI), serum ferritin (SF), serum transferrin (Tf), total iron binding power (TIBC) and serum hepcidin in the 3 groups before treatment (F<2.45, P>0.05). Compared with before treatment, the 3 groups of RBC, Hb, Hct, SI, SF, Tf, TIBC, and serum hepcidin were significantly improved (T>2.141, all P<0.05), and the difference between the 3 groups was statistically significant (3.57, 0.05). The RBC, Hb, Hct, SI, SF, Tf, TIBC and serum hepcidin of the combined treatment group were significantly higher than that of the Chinese herb group and the niferex group (T>2.16, P<0.05), and see table 2. Chinese medicine diagnosis and syndrome differentiation criteria refer to the diagnostic criteria of TCM syndromes and the symptoms before and after treatment are compared with those shown in table 3.

Comparison of adverse reactions

In the course of treatment, the function of heart, liver and kidney of the 3 groups were in the normal range. There were 3 cases of gastrointestinal symptoms (abdominal distention, nausea and loss of appetite) in the caulis group. The incidence of adverse reactions was 5%. There were 8 cases of gastrointestinal symptoms (abdominal distention, nausea, loss of appetite) in the niferex group. The incidence of adverse reactions was 13.3%. There were 10 cases of gastrointestinal symptoms (abdominal distention, nausea and loss of appetite) in the combined treatment group, and the incidence of adverse reactions was 16.6%.

The incidence of adverse reactions between the 3 groups was statistically significant ($\chi^2 = 5.128$, $P < 0.05$), and the results were shown in table 4.

DISCUSSION

Iron deficiency anemia is an anemia caused by hemoglobin synthesis hindered by the lack of iron elements in the body (Balmadrid *et al.*, 2015). The main clinical manifestation is the abnormal reduction of hematocrit, hemoglobin and red blood cell count in circulating blood compared with the normal standard.

Table 1: Comparison of clinical efficacy

| Group | Number of cases | Recovery | Obvious effect | Number of cases | Recovery | Obvious effect |
|--------------------------|-----------------|----------|----------------|-----------------|----------|----------------|
| Caulis group | 60 | 25 | 17 | 16 | 4 | 93.33 |
| Niferex group | 60 | 28 | 15 | 13 | 3 | 95.0 |
| Combined treatment group | 60 | 35 | 15 | 9 | 1 | 98.3 |

Table 2: Comparison of laboratory indexes

| Group | Time | RBC(*1012/L) | Hb(g / L) | Hct(%) | SI($\mu\text{mol} / \text{L}$) |
|--------------------------|------------------|--------------------------------|----------------------------------|----------------------------|------------------------------------|
| Caulis group | Before treatment | 2.84±0.27 | 81.59±13.28 | 28.41±5.14 | 6.05±1.57 |
| | After treatment | 3.92±2.56 | 103.57±18.92 | 33.24±6.15 | 8.14±1.85 |
| Niferex group | Before treatment | 3.15±0.38 | 81.64±12.14 | 26.45±4.87 | 5.83±1.61 |
| | After treatment | 3.48±2.16 | 115.34±15.21 | 30.21±5.18 | 8.45±1.92 |
| Combined treatment group | Before treatment | 2.89±0.35 | 82.46±11.34 | 26.14±6.12 | 5.74±1.64 |
| | After treatment | 3.83±2.57 | 120.21±16.01 | 35.12±4.87 | 8.41±2.21 |
| Group | Time | SF($\mu\text{g} / \text{L}$) | Tf($\mu\text{mol} / \text{L}$) | TIBC ($\mu\text{mol/L}$) | Serum hepcidin ($\mu\text{g/L}$) |
| Caulis group | Before treatment | 12.31±3.68 | 59.31±4.12 | 74.28±13.64 | 18.61±9.46 |
| | After treatment | 18.46±3.45 | 45.12±2.47 | 61.23±11.24 | 31.24±10.83 |
| Niferex group | Before treatment | 11.27±2.61 | 54.25±3.57 | 76.18±12.35 | 22.64±12.31 |
| | After treatment | 15.52±3.12 | 42.15±2.19 | 63.48±9.15 | 30.28±11.24 |
| Combined treatment group | Before treatment | 12.24±2.75 | 56.12±6.41 | 75.42±14.12 | 21.12±10.61 |
| | After treatment | 16.12±3.02 | 41.02±3.48 | 54.10±10.22 | 41.36±11.84 |

Table 3: Comparison of the symptoms of traditional Chinese medicine before and after treatment

| Group | Time | Poor complexion | Lack of Appetite | Tiredness | Abnormality of lip and tongue color | Diarrhea |
|--------------------------|------------------|-----------------|------------------|-----------|-------------------------------------|-----------|
| Caulis group | Before treatment | 2.56±0.63 | 2.59±1.04 | 2.24±0.82 | 1.59±0.74 | 1.35±0.68 |
| | After treatment | 1.21±0.51 | 1.52±0.78 | 1.12±0.67 | 0.74±0.53 | 0.62±0.47 |
| Niferex group | Before treatment | 2.48±0.51 | 2.73±0.94 | 2.13±0.74 | 1.63±0.67 | 1.41±0.72 |
| | After treatment | 1.14±0.35 | 1.45±0.51 | 1.03±0.58 | 0.71±0.61 | 0.65±0.48 |
| Combined treatment group | Before treatment | 2.51±0.58 | 2.78±0.84 | 2.34±0.78 | 1.74±1.64 | 1.51±0.64 |
| | After treatment | 0.94±0.41 | 0.81±0.49 | 1.13±0.48 | 0.41±0.21 | 0.45±0.13 |

Table 4: Adverse reaction

| Group | Vomit | Abdominal distention | Abdominal pain | Nausea | Loss of appetite | Incidence of adverse reactions |
|--------------------------|-------|----------------------|----------------|--------|------------------|--------------------------------|
| Caulis group | 0 | 1 | 0 | 1 | 1 | 5.0% |
| Niferex group | 2 | 1 | 0 | 2 | 3 | 13.3% |
| Combined treatment group | 1 | 2 | 1 | 4 | 3 | 16.6% |

With the change of lifestyle and dietary structure, the incidence of the disease has been increasing in recent years, which has caused serious impact on the quality of life and health of the patients (Kargulewicz *et al.*, 2016). Microelement iron preparation is a common drug for the treatment of iron deficiency anemia, including two types of organic iron and inorganic iron (Ghoneum *et al.*, 2015). Among them, ferrous sulfate is widely used in clinical treatment with the advantages of being absorbed easily in the duodenum, rich in drug sources and low in cost. Although it can achieve certain curative effect, it is easy to cause diarrhea, constipation and other adverse reactions, which has adverse effects on the prognosis and quality of life of patients (Giorgi *et al.*, 2015). It is an organic compound of iron and low molecular polysaccharides, and does not contain any free iron ions. Although its toxic and side effects are less than ferrous sulfate, it can still lead to gastrointestinal side effects.

Iron deficiency anemia shows the physical characteristics as “weak and tired” and “blood deficiency” in traditional Chinese medicine, while the caulis has the effect of passing through the meridian, activating blood and enriching blood and so on (Huang *et al.*, 2016). It is widely used in the treatment of numbness, irregular menstruation and blood deficiency, and the curative effect is accurate (Gunaldi *et al.*, 2015). The related experiments confirmed that the ravage index, red cell volume, hemoglobin and red blood cell level were significantly improved, and the proliferation of late hematopoietic progenitor cells and early erythroid progenitor cells could be stimulated. In addition, CV can improve the red blood cell count and hemoglobin level in hemolytic anemia and hemolytic anemia caused by cyclophosphamide and acetyl phenyl hydrazine, and improve the iron deficiency of the body (Larsen *et al.*, 2013). The results of this study showed that the total effective rate of the combined treatment group and the blood serum levels of hepcidin and total iron binding force after treatment were significantly better than those in the other groups, and the incidence of adverse reactions in the Chinese medicine group was lower than that of the other groups. In this study, it is suggested that the effect of the decoction of *Caulis* in the treatment of ischemic anemia on the basis of oral iron agent is better than that of oral iron only, and the improvement of blood related indexes is more significant.

Hepcidin is a key hormone in the regulation of iron homeostasis (Inzucchi *et al.*, 2015). It is an antibacterial polypeptide synthesized by the liver. In anemic state, the expression of hepcidin in the body is significantly decreased, which leads to the increase of iron absorption in the small intestine and the increase of iron release from the macrophage. It is reported that the serum hepcidin level of IDA patients is significantly lower than that of normal persons (Jean *et al.*, 2017). This study found that caulis could significantly increase the serum hepcidin. Therefore, Chinese medicine *Caulis* has created the

concept of hepcidin daily diet health preservation (Cardaropoli *et al.*, 2015). That is, it is an effective and safe innovative method to improve iron metabolism disorder by ingesting the functional foods targeting hepcidin and its regulatory proteins.

Modern pharmacological studies have also confirmed that CB has the effect of increasing red blood cells, hemoglobin (Hb), red cell volume (MCV) and red cell division index, which can stimulate the proliferation of early erythroid progenitor cells (BFU-E) and advanced hematopoietic progenitor cells (CFU-E), and can make acetyl phenyl hydrazine (APH) and cyclophosphamide (CY). RBC and Hb in hemolytic anemia and hemorrhagic anemia mice were significantly increased and even close to normal values. The total number of nucleated cells in bone marrow of mice caused by APH and CY decreased, and the formation of erythropoietin (EPO) was promoted. The mechanism of its action to erythropoietin cells may be used to promote the secretion of EPO like growth factor or increase EP by T lymphoblastic cells (Michels *et al.*, 2015). The activity of O like growth factor is related. In this study, IDA patients were treated with 3 different treatments, such as niferex, *Caulis* and combinatorial pattern. The results showed that Chinese herbal medicine caulis can significantly improve the number of red blood cells, hemoglobin, hematocrit and related iron metabolism, but the improvement of the combined treatment group was more obvious. There was no significant difference in the recovery rate between the caulis group and the niferex group, but the recovery rate of the combined treatment group was significantly higher than that of the Chinese herb group and the niferex group, and the function of the heart, liver and kidney in the *Caulis* group was in the normal range. The results showed that *Caulis* could significantly improve the clinical symptoms and iron metabolism indexes of IDA patients, but the combined effect was better.

CONCLUSION

This study found that *Caulis* could significantly increase the serum hepcidin. Therefore, caulis has created the concept of hepcidin daily diet health preservation. That is, it is an effective and safe innovative method to improve iron metabolism disorder by ingesting the functional foods targeting Hepcidin and its regulatory proteins. To sum up, Chinese herb caulis extract caulis can significantly improve the clinical symptoms and iron metabolism of patients with iron deficiency anemia, and the effect of combined oral iron are better. In conclusion, the decoction of *Caulis* in combination with oral iron is effective in the treatment of iron deficiency anemia patients. It can effectively improve the level of blood related indexes and improve the therapeutic effect. *Caulis* has certain clinical value.

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