IJMS
Vol 42, No 1, January 2017

Brief Report

# Comparison of the Effects of Iron Oxide, as a New Form of Iron Supplement, and Ferrous Sulfate on the Blood Levels of Iron and Total Iron-Binding Globulin in the Rabbit

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Received: 29 July 2015
Revised: 17 November 2015
Accepted: 13 December 2015

## What's Known

- Iron oxide is an important biological agent that has a key role in medical processes and used as iron supplements.

## What's New

- Although the role of iron oxide in medical processes is known, however, the mechanism of providing iron for biological usage was unclear. Our results clarified the effect of oral iron oxide on serum iron status and related parameters.

## Abstract

Iron oxide is an important biological agent that has a key role in medical processes; however, the mechanism whereby it provides iron for human and animal cells and its biological uses remains unclear. We aimed to evaluate the effects of oral iron oxide on serum iron status and compare the results with those of iron sulfate as a reference salt. Fifteen adult rabbits were divided into 3 groups of 5 each: control group, iron sulfate group, and iron oxide group. The groups received doses of 3.3, 10, and 33 mg/kg in 3 experiments. Venous blood samples were obtained just before the oral administration of iron sulfate and iron oxide (3.3 mg/kg). More blood samples were taken 3 times at the time points of 1, 6, and 12 hours after the administration of the solutions. Serum was separated for the measurement of iron (Fe) and total iron-binding globulin (TIBG) with routine methods. One week later, the same experiment was repeated with 10 mg/kg of iron sulfate and iron oxide; and 1 week later after the second experiment, again the same experiment was repeated with 33 mg/kg of iron sulfate and iron oxide. The results showed that 33 mg/kg of iron sulfate 1 hour after treatment caused a significant difference in the Fe and TIBG levels between all the groups (P=0.014 for Fe and P=0.027 for TIBG). Our data showed that the absorption of iron oxide was similar to that of ferrous sulfate and in high doses was as useful as iron supplement.

Please cite this article as: Kheiri R, Koohi MK, Sadeghi-Hashjin G, Nouri H, Khezli N, Hassan MA, Hoomani F, Shams GhR, Rasouli A, Motaghinejad M. Comparison of the Effects of Iron Oxide, as a New Form of Iron Supplement, and Ferrous Sulfate on the Blood Levels of Iron and Total Iron-Binding Globulin in the Rabbit. Iran J Med Sci. 2017;42(1):79-84.

**Keywords** ● Ferric oxide ● Rabbit ● Blood iron ● Ferrous sulfate

## Introduction

Iron, one of the most abundant metals on earth, is essential for the physiology of erythrocytes and is an integral part of some enzymes and proteins involved in oxygen transfer in organisms.[1,2] Iron deficiency is the most common cause of chronic anemia. Iron sulfate is one of the iron salts and is available as a medicine preparation for the clinical indications of iron consumption such as the treatment for or prevention of iron deficiency anemia.[3-5] However, due to the side effects of ferrous sulfate, some new formulations of iron supplement are under investigation and are being considered for the replacement of ferrous sulfate. One of these new agents is iron oxide. This therapeutic supplement has a widespread application,

and previous studies have shown that in addition to providing blood iron (Fe) for microorganism cells, this agent can act as an antioxidant compound. Iron oxide plays a key role in biomedicine and can act as an iron supplement.[6] Iron oxide is a metallic oxide, with numerous functions in scientific and industrial affairs.[2] Accordingly, we sought to evaluate the effects of iron oxide, as a new form of iron supplement, on Fe and total iron-binding globulin (TIBG) levels, and compare them with those of iron sulfate, as a standard available iron supplement. Rabbits were used as an experimental model as the size of the animal allowed serial blood collections.

## Materials and Methods

Animals: In the present study, 15 white New Zealand adult male rabbits weighing about 2 kg were obtained from Razi Research Institute. The rabbits were kept in cages at the Laboratory Animal Husbandry Center, Faculty of Veterinary Medicine, University of Tehran.

Chemicals: Iron sulfate solution and iron oxide (3.3, 10, and 33 mg/kg) were obtained from Merck Company and were prepared based on previous studies.[1,2]

Experimental Design: The rabbits were randomly divided into 3 groups, each group containing 5 rabbits: control group (receiving water), iron sulfate solution group, and iron oxide solution group.

First Experiment: On the first day after a 1-week adaptation period, the solutions at a concentration of 3.3 mg/kg were drenched to the rabbits by gavage. For this purpose, the rabbits were removed from their cages and weighed. Next, they were physically restrained and blood samples were taken from their jugular or ear marginal veins. Subsequently, one of the mentioned solutions was drenched to the animals as 1 mL/kg of the solution with a concentration of 3.3 mg/kg, while the control group received only water. Furthermore, at the time points of 1 hour, 6 hours, and 12 hours after the iron solution administration, blood samples were again obtained and Fe and TIBG levels were measured.

Second Experiment: One week after the first experiment, the second experiment was commenced. In this phase, the rabbits were drenched with the iron solutions (10 mg/kg at 1 mL/kg), and blood samples were taken in the same manner as the previous experiment. The levels of Fe and TIBG were measured with a Hitachi AutoAnalyzer (Tokyo, Japan) in the lab.

Third Experiment: All the procedures were done in the same manner as the previous experiments, except for the dosage of the iron solutions (33 mg/kg at 1 mL/kg).

*Data Analysis*

The results of the biochemical tests in the control and the 2 experimental groups are presented as mean±SEM. The differences between the 3 groups at the above-mentioned time points were analyzed using the repeated measures and the Tukey HSD post-hoc test. Differences were considered significant when $P<0.05$.

## Results

*Results of the Fe Level*

The Fe levels in the control and treatment (iron sulfate and iron oxide) groups were recorded in the first (3.3 mg/kg), second (10 mg/kg), and third (33 mg/kg) experiments at time 0 and 1 hour, 6 hours, and 12 hours following iron supplement administration. Our data showed that at time 0, there were no significant differences in the Fe level between the study groups ($P=0.054$). Nevertheless, at time 0, there were statistically significant differences between the groups receiving 3.3 mg/kg and 10 mg/kg of iron sulfate and iron oxide and the groups under treatment at a dosage of 33 mg/kg ($P<0.001$ and $P=0.014$, respectively). One hour later, there were significant differences in the Fe level between the treatment groups ($P=0.007$), and there were no significant differences ($P=0.205$) between the groups receiving the mentioned doses of iron compounds. Six hours later, there were no significant differences in the Fe level between the treatment groups ($P=0.771$), and there were significant differences between the groups under treatment at a dosage of 3.3 mg/kg and the groups under treatment at a dosage of 33 mg/kg ($P=0.014$). The measurement of the Fe level 12 hours later showed no significant differences between the treatment groups at this time point ($P=0.702$), and there were no significant differences ($P=0.377$) between the groups under treatment at the different doses (3.3, 10, and 33 mg/kg) (table 1).

*Results of the TIBG Level*

Our data showed that at time 0, there were significant differences in the TIBG level between the treatment groups ($P=0.021$) and there were significant differences between the groups under treatment at a dosage of 3.3 mg/kg and the groups under treatment at a dosage of 33 mg/kg ($P=0.027$). The TIBG level 1 hour later showed significant differences between the 3 groups (control, iron sulfate, and iron oxide) at this time point ($P=0.008$). The measurement of the TIBG

**Table 1:** Blood iron levels (µg/d) following the administration of iron sulfate and iron oxide at the doses of 3.3, 10, and 33 mg/kg at the time points of 0, 1, 6, and 12 hours following treatment

| Group | Dosage | Mean±SD | N |
|---|---|---|---|
| Fe1 | | | |
| Control | 3.3 mg/kg | 203.66±13.41 | 5 |
| | 10 mg/kg | 173.27±21.41 | 5 |
| | 33 mg/kg | 132.65±54.78 | 5 |
| | Total | 169.86±44.12 | 15 |
| Iron sulfate | 3.3 mg/kg | 236.60±40.58 | 5 |
| | 10 mg/kg | 223.40±47.28 | 5 |
| | 33 mg/kg | 182.00±58.70 | 5 |
| | Total | 214.00±51.70 | 15 |
| Iron oxide | 3.3 mg/kg | 234.00±27.83 | 5 |
| | 10 mg/kg | 212.40±54.26 | 5 |
| | 33 mg/kg | 153.20±36.64 | 5 |
| | Total | 199.86±51.92 | 15 |
| Total | 3.3 mg/kg | 224.75±31.35 | 15 |
| | 10 mg/kg | 203.02±45.90 | 15 |
| | 33 mg/kg | 155.95±51.62 | 15 |
| | Total | 194.57±51.71 | 45 |
| Fe2 | | | |
| Control | 3.3 mg/kg | 248.35±19.94 | 5 |
| | 10 mg/kg | 179.07±49.89 | 5 |
| | 33 mg/kg | 147.30±78.95 | 5 |
| | Total | 191.57±67.17 | 15 |
| Iron sulfate | 3.3 mg/kg | 268.40±52.35 | 5 |
| | 10 mg/kg | 279.20±66.60 | 5 |
| | 33 mg/kg | 268.40±37.50 | 5 |
| | Total | 272.00±49.80 | 15 |
| Iron oxide | 3.3 mg/kg | 244.80±12.89 | 5 |
| | 10 mg/kg | 224.20±42.77 | 5 |
| | 33 mg/kg | 203.20±136.75 | 5 |
| | Total | 224.06±78.88 | 15 |
| Total | 3.3 mg/kg | 253.85±32.55 | 15 |
| | 10 mg/kg | 227.49±65.55 | 15 |
| | 33 mg/kg | 206.30±100.74 | 15 |
| | Total | 229.21±72.94 | 45 |
| Fe3 | | | |
| Control | 3.3 mg/kg | 241.33±51.92 | 5 |
| | 10 mg/kg | 184.17±22.95 | 5 |
| | 33 mg/kg | 187.75±20.74 | 5 |
| | Total | 204.42±42.13 | 15 |
| Iron sulfate | 3.3 mg/kg | 208.60±42.05 | 5 |
| | 10 mg/kg | 230.40±57.61 | 5 |
| | 33 mg/kg | 202.20±46.91 | 5 |
| | Total | 213.73±47.31 | 15 |
| Iron oxide | 3.3 mg/kg | 224.20±52.74 | 5 |
| | 10 mg/kg | 229.20±30.57 | 5 |
| | 33 mg/kg | 144.40±16.07 | 5 |
| | Total | 199.26±52.46 | 15 |
| Total | 3.3 mg/kg | 224.71±47.55 | 15 |
| | 10 mg/kg | 214.59±43.14 | 15 |
| | 33 mg/kg | 178.11±38.36 | 15 |
| | Total | 205.80±46.79 | 45 |
| Fe4 | | | |
| Control | 3.3 mg/kg | 180.84±51.24 | 5 |
| | 10 mg/kg | 148.83±13.32 | 5 |
| | 33 mg/kg | 165.54±55.03 | 5 |
| | Total | 165.07±43.00 | 15 |
| Iron sulfate | 3.3 mg/kg | 161.60±26.16 | 5 |
| | 10 mg/kg | 167.80±35.94 | 5 |
| | 33 mg/kg | 144.60±55.23 | 5 |
| | Total | 158.00±39.23 | 15 |
| Iron oxide | 3.3 mg/kg | 159.40±31.37 | 5 |
| | 10 mg/kg | 173.60±63.53 | 5 |
| | 33 mg/kg | 125.80±63.62 | 5 |
| | Total | 152.93±54.96 | 15 |
| Total | 3.3 mg/kg | 167.28±36.42 | 15 |
| | 10 mg/kg | 163.41±41.14 | 15 |
| | 33 mg/kg | 145.31±56.35 | 15 |
| | Total | 158.67±45.44 | 45 |

level 6 and 12 hours later indicated that there were no significant differences between the treatment groups at these time points (P=0.651 and P=0.712, respectively). Our data showed no significant differences regarding the TIBG level between the groups under treatment at the different doses (3.3, 10, and 33 mg/kg) of iron sulfate and iron oxide at the time points of 1, 6, and 12 hours following iron solution administration (table 2).

*Results of Weight Changes*

The results pertaining to weight in the control and treatment (iron sulfate and iron oxide) groups 1, 3, and 5 days later were recorded (10 mg/mL). As is shown in table 3, in comparison with the control group, iron oxide resulted in a slight increase in the rabbits' weight 1 day following administration, whereas a slight weight decline was recorded in the iron sulfate solution group 1 day after administration. The trend persisted for another 3 days; however, 5 days after administration, both treatment groups indicated a slight weight increase in comparison with the control group, with the difference not constituting statistical significance (table 3).

## Discussion

Iron sulfate causes some side effects after oral use; some new formulations of iron supplement have, therefore, been under investigation with a view to replacing ferrous sulfate.

According to the results of the present study, following the oral administration of iron mixtures

**Table 2:** Total iron-binding globulin (TIBG) levels (µg/d) following the administration of iron sulfate and iron oxide at the doses of 3.3, 10, and 33 mg/kg at the time points of 0, 1, 6, and 12 hours following treatment

| Group | Dosage | Mean±SD | N |
|---|---|---|---|
| TIBG1 | 3.3 mg/kg | 334.61±38.21 | 5 |
| Control | 10 mg/kg | 322.58±77.88 | 5 |
| | 33 mg/kg | 281.91±24.69 | 5 |
| | Total | 313.04±53.56 | 15 |
| Iron sulfate | 3.3 mg/kg | 308.96±61.46 | 5 |
| | 10 mg/kg | 282.22±38.60 | 5 |
| | 33 mg/kg | 253.20±72.16 | 5 |
| | Total | 281.46±59.56 | 15 |
| Iron oxide | 3.3 mg/kg | 287.78±44.23 | 5 |
| | 10 mg/kg | 306.60±40.13 | 5 |
| | 33 mg/kg | 248.22±32.82 | 5 |
| | Total | 280.86±44.28 | 15 |
| Total | 3.3 mg/kg | 310.45±49.48 | 15 |
| | 10 mg/kg | 303.80±53.98 | 15 |
| | 33 mg/kg | 261.11±46.96 | 15 |
| | Total | 291.78±53.82 | 45 |
| TIBG2 | 3.3 mg/kg | 315.95±58.89 | 5 |
| Control | 10 mg/kg | 273.94±23.89 | 5 |
| | 33 mg/kg | 231.56±25.71 | 5 |
| | Total | 273.82±51.13 | 15 |
| Iron sulfate | 3.3 mg/kg | 271.55±79.22 | 5 |
| | 10 mg/kg | 233.22±102.72 | 5 |
| | 33 mg/kg | 290.64±67.96 | 5 |
| | Total | 265.13±82.091 | 15 |
| Iron oxide | 3.3 mg/kg | 234.16±76.44 | 5 |
| | 10 mg/kg | 278.78±55.28 | 5 |
| | 33 mg/kg | 252.58±42.39 | 5 |
| | Total | 255.17±58.44 | 15 |
| Total | 3.3 mg/kg | 273.89±75.17 | 15 |
| | 10 mg/kg | 261.98±67.07 | 15 |
| | 33 mg/kg | 258.26±51.60 | 15 |
| | Total | 264.71±64.20 | 45 |
| TIBG3 | 3.3 mg/kg | 288.04±37.86 | 5 |
| Control | 10 mg/kg | 271.85±47.68 | 5 |
| | 33 mg/kg | 248.14±29.23 | 5 |
| | Total | 269.34±39.88 | 15 |
| Iron sulfate | 3.3 mg/kg | 268.38±78.91 | 5 |
| | 10 mg/kg | 261.48±57.96 | 5 |
| | 33 mg/kg | 291.72±30.53 | 5 |
| | Total | 273.86±56.43 | 15 |
| Iron oxide | 3.3 mg/kg | 263.76±64.36 | 5 |
| | 10 mg/kg | 283.09±51.49 | 5 |
| | 33 mg/kg | 315.96±102.92 | 5 |
| | Total | 287.60±73.92 | 15 |
| Total | 3.3 mg/kg | 273.39±59.08 | 15 |
| | 10 mg/kg | 272.14±49.50 | 15 |
| | 33 mg/kg | 285.27±66.18 | 15 |
| | Total | 276.93±57.62 | 45 |
| TIBG4 | 3.3 mg/kg | 301.34±32.98 | 5 |
| Control | 10 mg/kg | 363.33±120.80 | 5 |
| | 33 mg/kg | 241.23±46.69 | 5 |
| | Total | 301.97±88.12 | 15 |
| Iron sulfate | 3.3 mg/kg | 317.20±52.96 | 5 |
| | 10 mg/kg | 279.14±38.95 | 5 |
| | 33 mg/kg | 299.20±50.65 | 5 |
| | Total | 298.51±47.19 | 15 |
| Iron oxide | 3.3 mg/kg | 234.86±31.21 | 5 |
| | 10 mg/kg | 281.44±50.69 | 5 |
| | 33 mg/kg | 225.68±23.45 | 5 |
| | Total | 247.32±42.52 | 15 |
| Total | 3.3 mg/kg | 284.46±52.47 | 15 |
| | 10 mg/kg | 307.97±83.54 | 15 |
| | 33 mg/kg | 255.37±50.84 | 15 |
| | Total | 282.60±66.28 | 45 |

(*Contd...*)

**Table 2:** *(Continued)*

(iron sulfate and iron oxide), the Fe level with iron oxide was approximately as good as that with ferrous sulfate. The groups under treatment with iron sulfate and iron oxide showed a significant difference in the Fe levels at time 0 and 1 hour after treatment. Our repeated measure analysis showed that there were no statistically significant changes at the time points of 6 and 12 hours after treatment in each group. In addition, the results concerning the effects of the doses of the solutions on each treatment group showed statistically significant differences between the treatment of the animals with 3.3 mg/kg and 10 mg/kg of iron sulfate and iron oxide and that with 33 mg/kg of iron sulfate and iron oxide at the time points of 1 hour and 6 hours after the administration of the solutions (table 1). Based on these findings, it can be concluded that iron oxide and iron sulfate can be effective on the Fe level between 1 and 6 hours after treatment and that only high doses of the agent (33 mg/kg) can be effective on the Fe level. These results may be explained by the type of the mixture used and the production processes applied. Our findings confirm previous data inasmuch as they showed that the iron solutions used in the present study were not potent enough to increase the Fe level for up to 12 hours. It seems necessary that the dose of iron be repeated after 6 hours. These data showed that although iron oxide was as effective as iron sulfate in increasing the Fe level, its effect was dependent on time and dose. Likewise, at time 0 and at the time point of 1 hour after the administration of iron sulfate and iron oxide, there were statistically significant differences in the TIBG level between the groups under treatment with iron sulfate and iron oxide. Nonetheless, the measurement of the TIBG level at the time points of 6 and 12 hours following

**Table 3:** Weight changes (kg) on days 1, 3, and 5 following iron administration at a dose of 10 mg/kg

| Treatment | One day after administration | Three days after administration | Five days after administration |
|---|---|---|---|
| Control | 0.01±0.01 | 0.04±0.004 | 0.05±0.004 |
| Iron sulfate | -0.02±0.02 | 0.03±0.40 | 0.08±0.02 |
| Iron oxide | 0.040±0.02 | 0.0460.02 | 0.10±0.02* |

the administration of the solutions indicated that there were no significant differences between the groups under treatment with iron sulfate and iron oxide at these time points. Our results also indicated that the different doses of iron sulfate or iron oxide exerted no significant effects on the TIBG level at each measurement time (table 2). These data showed that although iron oxide was effective in increasing the TIBG level, its effect was dependent on time and not on the dose. This finding of the current study is consistent with some previous investigations showing the efficacy of oral iron bisglycinate and iron sulfate in preventing iron deficiency and anemia among pregnant women.[7] In another study, the use of iron sulfate and iron glycinate in anemic patients resulted in obvious improvement in mean corpuscular hemoglobin, serum iron, and ferritin but caused a reduction in transferrin. One study reported that iron sulfate conferred more beneficial effects than did another preparation.[8]

Based on the results of our study, there were significant differences in the TIBG level 12 hours after treatment between the groups under treatment with iron sulfate and iron oxide and the control group. However, our repeated measure analysis showed no statistically significant changes between time 0 and 1 hour and 6 hours after treatment with each supplement as well as the doses of each supplement (table 3). These data showed that although iron oxide could be as effective as iron sulfate in the management of the Fe level, its effect was independent of time.

Previous studies have demonstrated that lactoferrin is more effective than is iron oxide in the treatment of iron deficiency.[9] One study probed into the effects of supplementation with ferrous sulfate or iron bisglycinate chelate on ferritin concentration and reported positive effects in terms of a rise in ferritin concentrations in school children with low iron stores.[10] According to the findings of another study, tripeptide iron was an effective source of iron supplement for anemic rats with iron deficiency.[11] These studies suggest that ferrous bisglycinate chelate has similar efficacy, albeit with possibly lower gastrointestinal toxicity, to ferrous sulfate given at the conventional dose of 105 mg/d for the same time duration.[12] Many previous studies have demonstrated that iron deficiency can cause inflammatory diseases and increase oxidative stress in body organs. In contrast, some other previous studies have shown that ferrous sulfate can diminish these types of inflammatory diseases and increase oxidative stress.[13,14] On the other hand, some previous studies have reported that iron sulfate and iron oxide as well as other iron supplements can modulate body metabolism and body weight. Our results vis-à-vis weight gain are concordant with these results.[15,16]

## Conclusion

The implications of the findings of the present study are that perhaps iron oxide could be recommended as a supplementary compound to prevent or treat iron deficiency anemia. We suggest that this agent be used as an iron supplement or at least as an agent in combination with another standard agent. However, because of some limitations in the current study, we could not assess other hematological biomarkers such ferritin, and nor could we determine the usefulness as well as the pharmacokinetic and toxicokinetic effects of iron oxide. We would, therefore, recommend further studies on this topic.

## Acknowledgment

The authors would like to thank the Iranian Nanotechnology Initiative Council and the Faculty of Veterinary Medicine, University of Tehran, for their financial support.

**Conflict of Interest:** None declared.

## References

1. Umbreit J. Iron deficiency: a concise review. Am J Hematol. 2005;78:225-31. doi: 10.1002/ajh.20249. PubMed PMID: 15726599.
2. Liu K, Kaffes AJ. Iron deficiency anaemia: a review of diagnosis, investigation and management. Eur J Gastroenterol Hepatol. 2012;24:109-16. doi: 10.1097/MEG.0b013e32834f3140. PubMed PMID: 22157204.
3. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT.

Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. Transfusion (Paris). 2009;49:2719-28. doi: 10.1111/j.1537-2995.2009.02327.x. PubMed PMID: 19682342.
4. Bryant BJ, Yau YY, Arceo SM, Daniel-Johnson J, Hopkins JA, Leitman SF. Iron replacement therapy in the routine management of blood donors. Transfusion (Paris). 2012;52:1566-75. doi: 10.1111/j.1537-2995.2011.03488.x. PubMed PMID: 22211316; PubMed Central PMCID: PMC3690467.
5. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database Syst Rev. 2012;1:CD007857. doi: 10.1002/14651858.CD007857.pub2. PubMed PMID: 22258974.
6. Lavina B, Dera P, Kim E, Meng Y, Downs RT, Weck PF, et al. Discovery of the recoverable high-pressure iron oxide Fe4O5. Proc Natl Acad Sci U S A. 2011;108:17281-5. doi: 10.1073/pnas.1107573108. PubMed PMID: 21969537; PubMed Central PMCID: PMC3198347.
7. Milman N, Jonsson L, Dyre P, Pedersen PL, Larsen LG. Ferrous bisglycinate 25 mg iron is as effective as ferrous sulfate 50 mg iron in the prophylaxis of iron deficiency and anemia during pregnancy in a randomized trial. J Perinat Med. 2014;42:197-206. doi: 10.1515/jpm-2013-0153. PubMed PMID: 24152889.
8. Walczyk T, Kastenmayer P, Storcksdieck Genannt Bonsmann S, Zeder C, Grathwohl D, Hurrell RF. Ferrous ammonium phosphate (FeNH(4)PO(4)) as a new food fortificant: iron bioavailability compared to ferrous sulfate and ferric pyrophosphate from an instant milk drink. Eur J Nutr. 2013;52:1361-8. doi: 10.1007/s00394-012-0445-y. PubMed PMID: 22956195.
9. Rezk M, Dawood R, Abo-Elnasr M, Al Halaby A, Marawan H. Lactoferrin versus ferrous sulphate for the treatment of iron deficiency anemia during pregnancy: a randomized clinical trial. J Matern Fetal Neonatal Med. 2016;29:1387-90. doi: 10.3109/14767058.2015.1049149. PubMed PMID: 26037728.
10. Duque X, Martinez H, Vilchis-Gil J, Mendoza E, Flores-Hernandez S, Moran S, et al. Effect of supplementation with ferrous sulfate or iron bis-glycinate chelate on ferritin concentration in Mexican schoolchildren: a randomized controlled trial. Nutr J. 2014;13:71. doi: 10.1186/1475-2891-13-71. PubMed PMID: 25023784; PubMed Central PMCID: PMC4107593.
11. Xiao C, Lei X, Wang Q, Du Z, Jiang L, Chen S, et al. Effects of a Tripeptide Iron on Iron-Deficiency Anemia in Rats. Biol Trace Elem Res. 2016;169:211-7. doi: 10.1007/s12011-015-0412-6. PubMed PMID: 26109335.
12. Ferrari P, Nicolini A, Manca ML, Rossi G, Anselmi L, Conte M, et al. Treatment of mild non-chemotherapy-induced iron deficiency anemia in cancer patients: comparison between oral ferrous bisglycinate chelate and ferrous sulfate. Biomed Pharmacother. 2012;66:414-8. doi: 10.1016/j.biopha.2012.06.003. PubMed PMID: 22795809.
13. Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. Ann Gastroenterol. 2013;26:104-13. PubMed PMID: 24714874; PubMed Central PMCID: PMC3959949.
14. Puntarulo S. Iron, oxidative stress and human health. Mol Aspects Med. 2005;26:299-312. doi: 10.1016/j.mam.2005.07.001. PubMed PMID: 16102805.
15. Mahmoudi M, Hosseinkhani H, Hosseinkhani M, Boutry S, Simchi A, Journeay WS, et al. Magnetic resonance imaging tracking of stem cells in vivo using iron oxide nanoparticles as a tool for the advancement of clinical regenerative medicine. Chem Rev. 2011;111:253-80. doi: 10.1021/cr1001832. PubMed PMID: 21077606.
16. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine 18ed. Maidenhead: McGraw Hill Professional; 2011.