



An exclusionary approach to recover Iron deficiency by POLYROL: an over view of Iron Polymaltose complex.

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Abstract

The current review is based on Iron (III)-hydroxide polymaltose complex that shows that iron is meaningfully bioavailable after oral administration, especially in iron-deficient patients. Iron (III) - hydroxide polymaltose complex (IPC) is an iron preparation with non-ionic iron and polymaltose in a stable composite. Since past decades so many research organizations has conducted clinical trials in men, women, children and infants and have shown that IPC is effective in treating iron deficiency anaemia (IDA). Researchers concluded that because of its kinetic properties, IPC is best given with meals, and probably in an iron dose slightly higher than that of the classical iron salts. Furthermore in terms of acceptance and patient compatibility, IPC presents a clear benefit as compare to ferrous salts. So many research and published works have shown a lower rate of treatment interruption with IPC than with ferrous salts. This is usually associated with a lower incidence of adverse events related to the upper gastro intestinal tract.

Keywords: Iron (III) -hydroxide polymaltose complex (IPC), Iron deficiency, Anemia.

Introduction

Iron present in all cells of the human body, iron is a mineral that has several vital functions, while Iron is not like gold that glitters or silver that shines; however it outshines both in its biological importance^{1,2,3}. An adult human has roughly 3.5-5g of iron in their body and 65-70% of the iron in the body is referred to as 'transport. Iron iron'stores tha in Liver, bone-marrow, spleen and muscles approx. 25%, this called storage iron and approximately 4% is used within myoglobin and iron-containing enzymes this called functional iron. As the major part of hemoglobin in red blood cells, it carries oxygen from the lungs to all parts of the body and facilitates oxygen use and storage in muscles. Every cell in the body needs iron to produce energy^{2,4,5,6}.

Iron deficiency (ID) and iron-deficiency anemia (IDA) both are persist to be of globally concern. A recent estimate based on WHO criteria indicated that around 600- 700 million people worldwide have marked iron deficiency anaemia (IDA) and bulk of these people live in developing countries like India and Sri Lanka. Along with children in the developing countries, iron is the most common single-nutrient supplement deficiency¹. In industrialized counties, de-spite a demonstrable decline in prevalence 2 iron-deficiency anemia (IDA) remains a frequent reason of anemia in young children^{3,6,7}. On the other hand, even more important than anemia it is the indication that the more common Iron deficiency (ID) without anemia may also adversely affect long-term neurodevelopment and

behavior and that some of these effects may be permanent, because of the implications for pediatric health care providers and their patients, this report reviews and summarizes this information. Iron preparations like Ferrous Sulfate (FS), Iron Polymaltose Complex (IPC) and Carbonyl Iron are extensively prescribed for the prevention and treatment of Iron deficiency anemia. Orally administered Ferrous Sulfate, the least expensive among these preparations, is the treatment of choice for Iron deficiency anemia^{1,4,6,7,8}.

Hemoglobin^{1,2,3,4,5,6,-} Hemoglobin is the protein molecule in red blood cells that carries oxygen from the lungs to the body's tissues and returns carbon

dioxide from the tissues back to the lungs. Hemoglobin plays a significant responsibility in maintaining the shape of the red blood cells. In their natural shape, red blood cells are round with narrow centers resembling a donut without a hole in the middle. Abnormal hemoglobin structure can, therefore, disrupt the shape of red blood cells and impede their function and flow through blood vessels.

The hemoglobin level is expressed as the amount of hemoglobin in grams (gm) per deciliter (dL) of whole blood, a deciliter being 100 milliliters. The normal ranges for hemoglobin depend on the age and, beginning in adolescence, the gender of the person.

Table -1 showing normal and required Hemoglobin in human body with respect to the ages 4,5,6,7,8,9,10.

S. No	Terms in ages	Normal range of Hemoglobin
1	Newborns:	17 to 22 gm/dL
2	One (1) week of age	15 to 20 gm/dL
3	One (1) month of age	11 to 15gm/dL
4	Children	11 to 13 gm/dL
5	Adult males	14 to 18 gm/dL
6	Adult women	12 to 16 gm/dL
7	Men after middle age	12.4 to 14.9 gm/dL
8	Women after middle age:	11.7 to 13.8 gm/dL

Table-2 showing differences between bivalent and trivalent oral iron preparations^{2,3,4,6,8,10.}

S. No	Iron Supplement	Comment
1	Ferrous fumarate (Fe ²⁺)	More adverse effects if not in a prolonged-release formulation
2	Ferrous gluconate (Fe ²⁺)	
3	Bivalent Ferrous sulphate (Fe ²⁺)	
4	Ferrous glycine sulphate (Fe ²⁺)	
5	Trivalent- Iron protein succinylate (Fe ³⁺)	Poorer absorption, More expensive
7	Iron polymaltose complex (Fe ³⁺)	A greater number of intakes

Anemia^{11,12,13,14,15.}: The condition of having a lower-than-normal number of red blood cells or quantity of hemoglobin. Hemoglobin (Hb) concentration 2 SDs below the mean Hb concentration for a normal population of the same gender and age range, as defined by the World Health Organization, the United Nations Children'sited Nations University Fund,.On and the basis Un of the 1999–2002 US National Health and Nutrition Examination Survey, anemia is defined as a Hb concentration of less than 11.0 g/dL for both male and female children aged 12 through 35 months. For certain populations (ie, people living at high altitudes), adjustment of these values may be necessary. Children with chronic anemia are prone to infections and learning problems. The main causes of anemia are bleeding, hemolysis (excessive destruction of red blood cells), underproduction of red blood cells (as in bone marrow diseases), and underproduction of normal hemoglobin (as in sickle cell anemia and in iron deficiency anemia). Women are more likely than men to have anemia because of menstrual blood loss. In children, anemia is most commonly due to insufficient iron in the diet.

Iron deficiency^{1,2,3,6,9,10,12,13,14} - A state in which there is insufficient iron to maintain normal physiologic functions. When a person has used up the iron stored i deficiency doesn't always result in anemia, but i weakened immune system. Iron deficiency occurs when the diet does not include enough iron rich foods, if there is blood loss, or if there is an increased need for iron in the body, such as during adolescence and pregnancy. ID results from inadequate iron absorption to accommodate an increase in requirements attributable to growth or resulting from a long-term negative iron balance. Either of these situations leads to a decrease in iron stores as measured by serum ferritin (SF) concentrations or bone marrow iron content. ID may or may not be accompanied by IDA.

Iron-deficiency anemia^{1,3,15,16,17,18} -Iron deficiency anemia is diminished red blood cell production due to low iron stores in the body. It is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases. Iron deficiency anemia can consequence from inadequate iron intake, decreased iron absorption, increased iron demand, and increased iron loss. Identifying the underlying etiology and administering the appropriate therapy are keys to the evaluation and management of this condition. Diagnose of iron deficiency anemia^{19,20,21.}

Red blood cell size and color. With iron deficiency anemia, red blood cells are smaller and paler in color than normal.

Hematocrit. This is the percentage of your blood volume made up by red blood cells. Normal levels are generally between 34.9 and 44.5 percent for adult women and 38.8 to 50 percent for adult men. These values may change depending on your age.

Hemoglobin. Lower than normal hemoglobin levels indicate anemia. The normal hemoglobin range is generally defined as 13.5 to 17.5 grams (g) of hemoglobin per deciliter (dL) of blood for men and 12.0 to 15.5 g/dL for women. The normal ranges for children vary depending on the child's age and sex.

Ferritin. This protein helps store iron in your body, and a low level of ferritin usually indicates a low level of stored iron.

Eating Heme and Non-Heme Iron^{1,4,7,9,10}

There are two types of iron: heme and non-heme iron.

(a). Heme Iron — This form of iron comes from animal sources, such as red meat, and makes up about 10% of the dietary iron most people ingest. Heme iron is more easily absorbed.²

(b). Non-heme Iron — Non-heme iron comes from a variety of other sources, making up the remaining 90% of dietary iron. Non-heme iron is more difficult for the body to absorb. Absorption is facilitated by ascorbic acid, or other sugars and acids that help increase the iron's solubility.²

Challenges in Non-Heme Iron Absorption^{2,4,6,7,9,10,21.}

Getting the right amount of iron isn't just about eating iron-rich foods; it can also mean eating them in the right combination. Certain foods can also increase or decrease the amount of non-heme iron your body absorbs.

IPC- Iron polymaltose complex (IPC)^{2,3,4,8,10,20,21}

Iron polymaltose complex (IPC) is a new complex or compound, which binds iron in its ferric form and

follows iron absorption, extremely alike to that of ferrous iron salt form.

Chemistry of IPC- The iron (III)-hydroxide polymaltose complex is also called as IPC is a macromolecular complex in which polynuclear ferric oxyhydroxide is complexed with polysaccharide groups. IPC have molecular weight about 52300 Dalton. It is highly water-soluble over a wide-ranging pH (from 1–14) it is stable and does not precipitate in an alkaline environment. It also does not react in vitro at pH 3–8 with chelating agents from food (e.g. phytic acid) or with drugs containing phenolic groups, e.g. tetracycline. IPC has a reduction potential of –332 mV; this ensures that it is not reduced in biological fluids and therefore will not provoke oxidative stress.

Safety profile of IPC –Whenever IPC has been compared with a classical iron salt, the incidence, and often the severity of adverse events was either similar or lower than that observed with ferrous salts. Compared with ferrous salts, IPC is non-toxic with LD50 values in mice and rats more than 10 times higher than those for ferrous sulphate. In long-term studies with dogs, IPC doses of up to 270 mg iron/kg/day for 52 weeks had no effect on any organ system. Furthermore, IPC is a non-ionic complex, which does not release any free radicals. It is thus deprived of all toxic effects found due to the release of free radicals in the ionized iron salts.

Absorption- The main pathway for Fe^{2+} absorption is passive diffusion throughout duodenal enterocytes and consequently, with higher dose, iron intoxication may occur. On the other hand, IPC is practically non-toxic, since iron is released from the complex gradually and is absorbed by active transport with rate determining competitive legend exchange. The active transport is energetically dependent. Iron is therefore maximally absorbed when administered with or after meals. Food components such as phytic acid, tannin, soy bean flour, oxalic acid, sodium alginate, and tetracycline in the gastrointestinal tract may react with iron (II) or iron (III) salts giving rise to non-absorbable iron complexes and thus decreasing the concentration of bio-available iron. Since there is no interference between IPC and feed components, the bioavailability is not negatively influenced.

Bioavailability of IPC The bioavailability and efficacy of IPC has been evaluated by several authors with variable results. Several studies in human medicine have demonstrated high efficacy and safety of IPC in the treatment of anemia. For instance, in

blood donors, side effects were less frequent with IPC when compared with ferrous sulphate. According to Jacobs a scientist, the iron absorption from ferrous salts and IPC is quantitatively equivalent, in both experimental animals and human subjects. Few Scientist found that in terms of efficacy (higher Hb), IPC was superior to ferrous fumarate in the treatment of iron deficiency anemia. In our study, we have found a comparable efficacy of IPC in the anemia prevention with ferrous fumarate. Few studies show that ferrous salts and IPC have comparable effects in the treatment of iron deficiency anemia.

Clinical trials- Tuomainen *et al.* conducted a 6-month placebo-controlled trial in 48 men with serum ferritin 30 $\mu\text{g/L}$. Patients were rando plus placebo resembling FeSO_4 , microencapsulated FeSO_4 (180 mg of iron) plus placebo IPC, or both placebo.

After 6 months' time, serum period ferritin concentrations had increased 2.2-fold in the FeSO_4 group ($p < 0.001$) and 1.3- fold in the IPC group ($p < 0.001$ versus placebo). Erythrocytic ferritin, however, increased equally under both active treatments. Haemoglobin also increased in both groups (by 1.0 % with FeSO_4 and by 2.2 % with IPC, $p < 0.001$ vs placebo in both cases) (Fig. 4). Three subjects receiving 180 mg of iron as microencapsulated ferrous sulphate and 2 receiving 200 mg of iron as IPC reported gastric disturbances. This resulted in treatment discontinuation in one case in each group, while the dose was halved for the other three subjects.

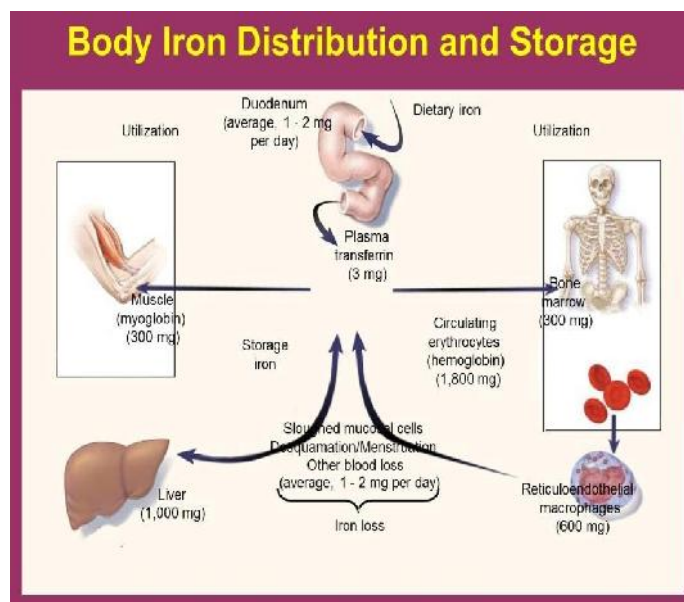


Figure-1 Pathways of Iron in the human body. Intake, storage and distribution throughout the organs.

Conclusion

A recent WHO report estimates the anemia prevalence among pregnant women to be 55.9% globally⁴. During pregnancy, anemia has a significant impact on the health of both the fetus as well as that of the mother. The treatment of IDA is directed at improving hemoglobin and compensating for the deficit in stored iron by supplying sufficient iron. In iron polymaltose complex, the elemental form is in a nonionic state. This causes less or no gastric irritation with iron polymaltose complex. In addition, the high elemental iron content of IPC eliminates the need for frequent dosing and therefore improves compliance. A study by Patkar and colleagues also demonstrated efficacy and safety of IPC, in both pregnant and non-pregnant women, but this was an open, uncontrolled trial. In another study, done by Rajadhyaksha, the efficacy and tolerability of IPC in IDA during pregnancy in Indian women were evaluated, and IPC was found to result in significantly reduced symptoms of anemia and significant improvements in serum iron, iron binding capacity, and Hb; furthermore, only 8% of patients showed mild GI-related adverse effects. However, this study was limited by the absence of a control group. In the study undertaken by Reddy to evaluate the efficacy and safety of IPC in pregnant women with IDA, it was shown that the clinical parameters as well as biochemical parameters showed favorable changes with IPC. In summary, none of these studies compared compliance and cost of iron preparations, and were conducted in non-pregnant women. Increased incidence of adverse effects with FS may be due to release of free radicals, which leads to cell damage and cell death.

In conclusion, IPC is comparatively more effective in the treatment of iron deficiency anemia in patients including pregnant women. A superior tolerability profile to that of the conventional iron preparation (Ferrous sulphate) and an equivalent efficacy profile strongly suggest that it can be considered as a useful and alternative formulation for the treatment of IDA during pregnancy. An vital variance between IPC and ferrous salts is that the bioavailability is really increased when IPC is taken with meals, so this is the optional method of management.

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