Study of Coulter Indices After Oral & Parenteral Iron Therapy In Iron Deficiency Anaemia

Dr. Amol Hartalkar*, Dr. Sheetal Hartalkar**
*Associate Professor, Department of Medicine, Rural Medical College;
**Consultant Periodontologist, Rural Dental College, PIMS (DU), Loni, (Maharashtra), India

Abstract: <u>Background:</u> Nutritional iron deficiency anaemia is prevalent. It responds promptly to iron therapy. Parenteral iron therapy is considered to be better for rapid correction of anaemia, than oral form. <u>Methodology:</u> The haematological response, of 47 severely iron deficient patients, to orally administered iron was compared to that of 40 patients given parenteral iron sorbitol. The haematological response was assessed with the help of Coulter indices. <u>Results:</u> No significant difference in the rate of change of haematological parameters was observed in oral & parenteral form of iron therapy. <u>Conclusion:</u> Earliest response & completion of therapy both can be judged by Red cell Distribution Width (RDW) levels in either form of iron replacement. Red Blood Cells histogram best reflects an evolution of response and overt attainment of normal contours & placement reflects the adequacy of treatment. [Hartalkar A NJIRM 2016; 7(2):113-118]

Key Words: Coulter indices, Severe Iron deficiency Anaemia, Oral iron, Iron Sorbitol.

Author for correspondence: Dr. Amol Hartalkar, Department of Medicine, Rural Medical College, Pravara Institute of Medical Sciences(DU),P.O. Loni (Bk),Dist.Ahmednagar–413736 (Maharashtra) India. <u>Email:</u> amolhartalkar@gmail.com

Introduction: Iron deficiency is the most common nutritional deficiency worldwide [1]. Oral iron is the treatment of choice for uncomplicated Iron Deficiency Anaemia (IDA).

Iron stores get replenished early with parenteral iron therapy is a commonly agreed statement. The recommendation that parenteral iron be given as an alternative to blood transfusions in IDA also implies more rapid response to parenteral therapy [2]. Many physicians a priori expect iron by injection to correct IDA faster than oral iron.

However, the overall result from Studies [3-11] comparing efficacy of oral & parenteral forms of iron replacement therapy, were non-conclusive. Four [5-9] were in favour of parenteral iron therapy, three [3,4,6] suggested that both the forms of therapy were equally effective, whereas in two studies [10, 11] parenteral therapy was more effective in initial two weeks but afterwards efficacy of both was same.

The present study was designed to observe the response to oral iron replacement using coulter indices and to compare it with parenteral iron therapy in severe nutritional iron deficiency anaemia. The need of blood transfusion, amongst these patients was also noted.

Material and Methods: This prospective study was carried out in the Department of Medicine, rural tertiary care teaching hospital.

<u>Inclusion criteria:</u>

- Patient with Haemoglobin (Hb) equal to or less than 7gm/dl.

- Peripheral smear showing microcytic hypochromic picture with anisopoikilocytosis suggestive of iron deficiency anaemia.

- Coulter cell counter showing low Mean Corpuscular Volume (MCV), low Mean Corpuscular Haemoglobin (MCH) and narrow peaked Red Blood Cells (RBC) histogram with shift to the left.

<u>Exclusion criteria:</u>
- Patient with history of hemorrhage i.e. bleeding per vaginum, bleeding per rectum, malena or with stool occult blood positive.

- Peripheral smears showing dimorphic picture or iron deficiency anemia in association with hemolytic / renal / any other primary cause.

- Coulter cell counter showing RBC histogram Biphasic or with broad peak and very broad base indicating dimorphic anemia.

To define normality range, 200 normal subjects (100 males and females each) were picked up whose Hb, HCT, RBC count, MCV, MCH, RDW parameters were within normal limits and RBC histogram was showing sharp peak and narrow base (50-125 fl.). The median drawn for each parameter was considered as target to be achieved i.e. 100% achievement.

The study population consisted of 87 patients of severe nutritional iron deficiency anaemia, of which 40

received parenteral iron therapy (initially intramuscular 75 mg iron sorbitol per day for 10 days followed by 100 mg per day of oral elemental iron) and 47 received oral iron therapy (100 mg of elemental iron per day in 20 patients & 300 mg of elemental iron per day in 27 patients) till they achieved target median value of all coulter indices.

A detailed history & clinical examination was done, to exclude cases with bleeding and other causes of anaemia. Blood samples were sent for complete hemogram by cell counter.

Patients were called for follow up after 10, 20, 30, 60, 90, 120 days & beyond. On each follow up visit, complete hemogram by cell counter was repeated.

Studying the response:
The response to oral and parenteral iron therapy were studied individually as case studies and also as a group.

Case study: Every time the patient visited his Hb, HCT, RBC, MCV, MCH and RDW were calculated in terms of percentage of target median value and the graph was plotted.

Percentile curves - Four representative cases of different percentiles (around 2.5 gm%, 4 gm%, 5.5 gm% and around 7 gm% haemoglobin) were selected, at the initiation of therapy. The response was plotted on a graph. This enabled us to graphically compare the pace of response in different percentiles over the various follow-up intervals.

Group study
Mean plots - The group behaviour (by drawing mean) of each parameter, over the successive time span (1-15, 16-30, 31-45, 46-60, 61-75, 76-90, 91-120 & so on) was plotted.

The mean plots of those receiving 100 mg & 300 mg of elemental iron per day were graphically compared for the pace of response. The identical comparison of response was carried out between those receiving oral & parenteral replacement.

Statistical analysis:
The effect of treatment on the haemoglobin level, expressed as a percentage of ratios of the correction achieved by the end of every 15 days till 120 days & beyond were analyzed by following formula.

$$p = \frac{X_n - X_0}{X_{120} - X_0} \times 100$$

where X_0 denotes initial mean haemoglobin value, $X_{n1 \ to \ n7}$ denotes mean haemoglobin at end of 15, 30, 45, 60, 75, 90, 120 days of therapy respectively, X_{120} denotes mean haemoglobin at the end of 120 days of therapy.

This proportion was then subjected to unpaired students t-Test (considering p value <0.05 as significant) to detect whether the difference in both the forms of therapy is significantly different.

Result: *Early / brisk marrow response* is reflected in rising RDW, appearance of right shoulder in RBC histogram & peaking RBC count. First two indices are marker of reticulocytosis. Hb, HCT and MCV, MCH are last to follow. (Fig. 1)

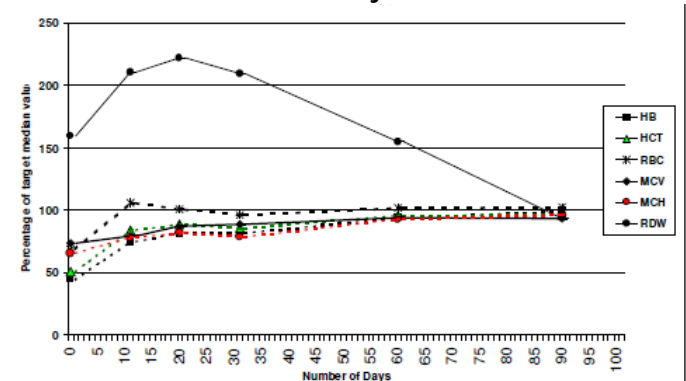**Figure 1: Typical response pattern after iron repletion in iron deficiency anaemia**

Figure 2: Haemoglobin response to 100 mg & 300 mg per day of oral elemental iron replacement was similar
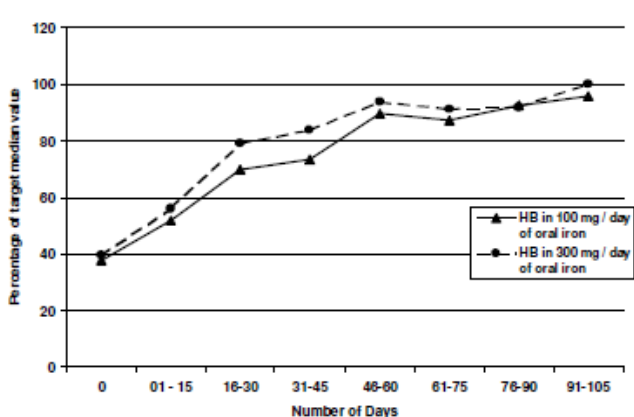
Figure 3: Response of haematological parameters to oral iron replacement (pooled data) & parenteral iron therapy was also similar.
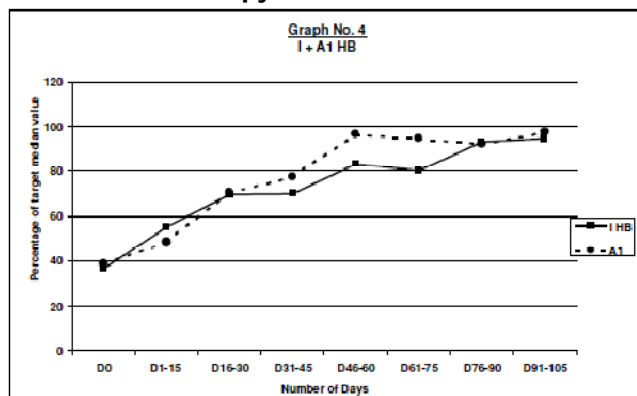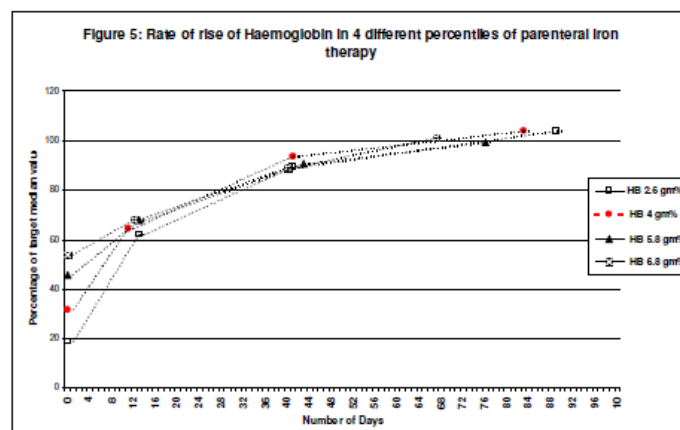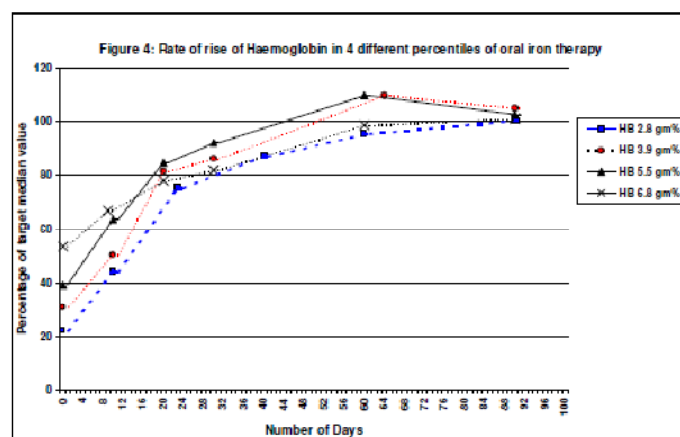

Graph No. 4
I + A1 HB

Table1: Typical response pattern after iron repletion therapy (Oral / parenteral)

Parameter	Pattern of response	Nature	Entry in normal range	Reaches target median value
RBC count	Slow rise	Consistent	15 days	Around 2 months
Hb, HCT	Slow rise	Consistent	60 days	Around 4 months
MCV	Slow rise	Consistent	60 days	Around 4 months
MCH	Slow rise	Consistent	45 days	Around 4 months
RDW	Initial rise, then steady decline	Consistent	120 days	Around 4 months
RBC histogram	Early widening of base & peak; then Gradual shift to right; then Late narrowing of base & peak	Consistent	10 days	Around 4 months
WBC count		Erratic	Not applicable	
Platelet count		Erratic	Not applicable	

The *adequacy* of replacement therapy can be judged by MCV falling in normocytic range and narrowing peak and base of RBC histogram. However, the final event is reflected in RDW settling to normal range. (Table 1)

The rate of rise of Hb is faster with lower Hb levels in the beginning. However, it takes around 4 months for these parameters to reach normal median value in all four percentile groups, i.e. the time span required to achieve normalcy is almost same, irrespective of the severity of anaemia. The response is the same for oral as well as parenteral iron (Fig.4 & 5).

Figure 4: Rate of rise of Haemoglobin in 4 different percentiles of oral iron therapy

Figure 5: Rate of rise of Haemoglobin in 4 different percentiles of parenteral iron therapy

Discussion: Studies all over the world[12] & in India[13] show that Iron Deficiency Anaemia (IDA) affects all age groups and both sexes.

In a rural setup, facilities for blood transfusion are not adequate. A physician thus has to depend upon either oral or parenteral form of iron therapy.

But, parenteral iron therapy has disadvantages like [14]: It may need hospitalization,

- Possibility of hypersensitivity reactions,
- Administration is painful (IM / IV / Intraperitoneal)
- Hyperpigmentation / discoloration of local skin area,
- Higher cost of total therapy.

Therefore, the most feasible option is oral iron replacement.

The issues at stake are,
- How quickly oral iron raises haemoglobin as compared to parenteral therapy?
- When is the blood transfusion indicated?

Our observations relate to nutritional severe iron deficiency anaemia. We found oral iron therapy as effective as parenteral iron replacement. The pace of rise of haemoglobin in response to 100 mg & 300 mg per day of oral elemental iron was similar.

Severely iron deficient patients were selected because rapid response to specific therapy is most important in this group & the maximally stressed bone marrow taxes greatest supply of iron for erythropoiesis. If oral therapy is to compete with parenteral, it must provide iron at a rate sufficiently rapid so that erythropoiesis will not be limited by insufficient iron. Our study indicates that oral iron can provide an adequate supply of iron; which was comparable to parenterally administered iron. The observation is supported by other studies [5, 7, 8, 9].

50-100 mg oral elemental iron is effective & haemoglobin rise reported with 50, 100 & 200 mg of elemental iron is similar[15]. Also with increasing dose of elemental iron per day, the percentage of estimated absorption of iron decreases [16]. Doses higher than this are not recommended as the results are not better & side effects, consequent noncompliance are more with higher doses[15].

We [17] did come across some cases of iron deficiency anaemia with proven depleted bone marrow iron stores, which did not respond briskly either to oral iron therapy or to parenteral iron replacement. These cases demanded long-term oral iron replacement for a favourable response. We labelled them as 'slow responder / partial iron resistance'.

Failure of brisk response to parenteral iron & favourable response to long-term oral iron replacement implies that our patients did not have an absorption defect. These cases belong to defective metabolism / defective bone marrow uptake of iron of unknown cause. It was not the absolute defect, because they partially responded to long-term iron replacement. In our setting, malabsorption of iron is not the factor of any concern.

Some studies [10,11] comparing response to oral & parenteral iron therapy showed that with parenteral iron, response is rapid only during initial two weeks; after which both oral & parenteral forms produce same rate of rise in hematological parameters.

The effect of initial differences in haemoglobin levels influences the rate of response during first few days of therapy. The more anaemic patients show rapid response. The difference between the groups lessens with time & effectively dies out by two months. Mild anaemias appear to need as prolonged therapy (4 months) as the more severe anaemias [18].

The coulter parameters indicating earliest response to therapy are overtly peaking RDW, rise in RBC count & Reticulocytosis (as evident from appearance of right shoulder to RBC histogram) within 10 days of therapy. Hb, HCT & MCV, MCH rise later. Various studies [19-24] showed that the duration of earliest change in hematological parameters to indicate response to iron therapy were, Reticulocyte count, RBC histogram = within 7 days of therapy; RBC count = 4 - 10 days of therapy; Hb, HCT = 7 - 10 days of therapy; MCV = 18 days of therapy.

Adequacy of treatment reflects best in attaining normocytic RBC histogram with sharp peak & narrow base, supported by RDW setting to normal. The time span required is 4 months irrespective of severity of anaemia at the initiation of therapy. In spite of severe anaemia (Hb=2.2 gm%) none of our patient developed congestive failure. Hence, we did not require blood transfusion.

It has been observed that[25], anaemia in iron deficiency diseases, unlike megaloblastic anaemia, is insidious in onset & there has been ample time for hemodynamic & other adjustments. Therefore, even when haemoglobin is very low, it is not necessary to give blood transfusion to raise haemoglobin even if patient is in congestive failure.

Only two specific indications for blood transfusion may be,[25]
- A pregnant female with severe IDA very near term,
- Patient with severe anaemia with angina / symptoms of cerebral hypoxia.

We also, agree with these observations.

Indications of parenteral iron therapy [14] thus appears to be,
- Demonstrated intolerance to oral iron
- Proven non-compliance of patient
- Proven malabsorption
- Need for rapid replenishment for iron stores with continuing severe blood loss.

Conclusion: It can be concluded that oral iron therapy is as effective as parenteral one even in severe Anaemia. It requires to be given for 12-16 weeks in all cases and peaking RDW and RBC count are best coulter indices for response assessment.

References:
1. Demeyer E, Adilis Tegmen M, Rayston E. 'The prevalence of anemia in world'. World health statistics 1984; 38:302-316.
2. Sportor, R.F. Intravenous Iron as alternate to blood transfusion in late pregnancy. Amer J Obstet Gynec 1957; 73: 338-340
3. McCurdy PR. Oral & parenteral iron therapy. JAMA 1965; 191(10): 155-158.
4. Pritchard JA. Response to iron in iron deficiency: Anemia due to gynecological disease JAMA 1961; 175: 478-482.
5. Al Momen AK, Al Meshari, Al Nuail, Saddique A et al Intravenous iron sucrose complex in treatment of iron deficiency & anemia during pregnancy. Eur J Obst & Gynecology Reprod Biol 1996; 69: 121-4.
6. Bayoumeu F. Iron therapy in iron deficiency anemia in pregnancy: Intravenous route versus oral route. American journal of Obst & Gynecology 2002;186 (3): 518-522.
7. Singh K, Yong YF, Kuperan P. A comparison between iron polymaltose complex & oral ferrous fumerate in the treatment of iron deficiency anemia in pregnancy. Eur J of Hematology 1998; 60: 119-124.
8. Kamolafe JO, Kuti O, Ijadunola KT. A comparative study between intramuscular iron dextran & oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy. Journal of Obst & Gynecology 2003: 123 (6) : 628-631
9. Ogunbode O, Oluboyede OA, Ayeni O The treatment of iron deficiency anaemia with a new intramuscular iron preparation (Ferastral). Scandinavian Journal of Haematology (1977) Suppl. 32: 364-371.
10. World Health Organisation (WHO) 1993 Prevention and treatment of anaemia. WHO / FHE / MSM / 93. Geneva.
11. Thompson RB & Proctor SJ. Iron deficiency. In: A short textbook of Haematology, edited by Thompson RB & Proctor SJ. 6th edition. Pp 160-177. Hong Kong, Longman group Ltd.
12. K Madhvan Nair NIN, 'Iron in health & disease' – A review. Gujarat medical journal 2000;57,(1):5-12.
13. Sheshadri S. Nutritional anaemia & malnutrition in south Asia, A regional profile. UNICEF - Regional office for health Asia, Kathmandu publication, 1997; No. 5: 75-124.
14. John F Wilkinson. Iron therapy Current therapeutics. Practitioner's section of Indian Journal of Medical research 1961; 187: 224-230.
15. Mehta BC. Optimal dose of oral iron for IDA. Drugs & therapeutics 1985; 1: 30-31.
16. Goodman & Gillman. Pharmacological basis of therapeutics. 9th edition publisher.
17. Amol Hartalkar. The study of coulter indices in response to oral iron replacement & its comparison with parenteral iron therapy in severe iron deficiency anemia. A thesis, 2004. (Unpublished data)
18. Swan HT, Jowett GH. Treatment of iron deficiency with ferrous fumerate. BMJ 1959; Vol. 1:781-787.
19. Bessman D. Erythropoeisis during recovery from iron deficiency - Normocyte & macrocyte. Blood Dec 1977; 50(6): 987-993.
20. Clark W, Maurice P, William Castle. Quantitative aspects of iron deficiency in hypochromic anemia. Journal of clinical investigation 1932; 11: 91.
21. Nils SE, Anderson MD. Clinical investigation on new intravascular hematinics. British medical journal 1961;29. Vol. 2: 21- 27.
22. Roger Hamstra, Mathew Block. Erythropoesis in response to blood loss in man. Journal of applied physiology 1969; 4:503-507.
23. Schocket Alan L, Hamstra Roger D, Block Mathew H. Intravenous iron dextrean in clinical medicine. JAMA 1980; 243 (17):1726-1733

24. Lane RS. Change in plasma transferrin level following administration of iron. British journal of haematology 1966; 12: 249-258.

25. Mehta BC. Quarterly medical review Jan-March 2001; 52: (1) Page 9.

Conflict of interest: None
Funding: None
Cite this Article as: Hartalkar A, Hartalkar S. Study of Coulter Indices After Oral & Parenteral Iron Therapy In Iron Deficiency Anaemia. Natl J Integr Res Med 2016; 7(2): 113-118