Research Paper

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Anaemia Of Chronic Disorders In Respiratory Infections With Iatrogenic Iron Over Loading During Treatment In Hospitalized Patients

Medical Science

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ABSTRACT

The anaemia is a very common haematological problem. It is primarily identified by haemoglobin estimation. The most common anaemia is iron deficiency anaemia (IDA) which is mostly due to deficient iron stage developed either due to blood loss or nutritional deficiency. The second most common type of anaemia is anaemia due to chronic disorders (ACD). This is the most common form of anaemia seen in hospitalized patients after the iron deficiency anaemia. The cause of ACD can be either infective, inflammatory, due to severe tissue injury or malignancy. The specific feature of this type of anaemia is hypoferremia with increased to high iron storage level in the form of serum ferritin.

The ACD superficially resembles the iron deficiency anaemia in which the iron storage in form of serum ferritin levels are always low to very low and the red cells are always microcytic hypochromic. While in the ACD due to the chronic disease there is sufficient or very high levels of body iron stores in form of serum ferritin and the red cells can be either normocytic normochromic or microcytic hypochromic. Although the both types of anaemia can be easily differentiated by the ferritin test but due to high cost of these tests the physicians mostly instead of identifying the type of anaemia they presume all the anaemias to be of iron deficiency origin. As such the ACD also are being treated by iron therapy or multiple blood transfusions and thereby creating the problem of iron overloading and inviting the ill effects of iron overloading complications like haemochromatosis.

A satisfactory answer to outcome of anaemia in this manner is not clear. The only remedy to this type of anaemia is to treat the cause of illness only. Because any negligence in identifying ACD from IDA can ultimately result to organ failure .

INTRODUCTION :

Respiratory disorders associated with ACD which have been studied are pulmonary tuberculosis, COPD, tubercular pleural effusion, pyothorax, and pneumonias. These chronic diseases when present for more than 1 or 2 months then they will mostly cause the ACD.

The anaemia is the result of deficient haemoglobin in red blood cells. It is formed by iron in mitochondria during development of red blood cells. The haemoglobin is the most important part which does the function of transporting oxygen from lungs to the peripheral tissues.

The anaemia occurs when either there is true iron deficiency or body iron which is although sufficient but is not made available to the red cells in bone marrow.

The ACD is the most common anaemia in world after the iron deficiency anaemia. The both can be easily differentiated by various iron test , GBP and bone marrow examination.

Basically the iron is a important element for every living cell life and also for the bacteria (causing the disease) for the purpose of survival and multiplication. So on the entry of bacteria a defensive mechanism is activated which induce cytokine interleukin -6 production. This interleukin -6 induce the production of hepcidin by the liver. The hepcidin induce the phagocytosis of all the available iron in body by the macrophages. The hepcidin also causes blockage of ferroportin present in enterocytes, hepatocytes and macrophages. Therefore the iron absorption is stopped and iron is not released. The macrophages do not supply iron even to the developing erythrocytes causing anaemia.

So there is hypoferremia in the presence of sufficient iron in the body. Therefore haemoglobin is not formed in sufficient quantity and the result is either normocytic normochromic or microcytic hypochromic red cells formation with low to very low haemoglobin levels.

We designate a patient to be anemic when the RBC count is <4.5 million in males and <4 million in females. Or we can also say that a person is anemic when haemoglobin concentration in males is <13 gm/dl or <12 gm/dl in females.

The clinical features of anaemia are like paleness, tiredness, weakness, oedema, and anorexia and various systemic effects.

We have studied various values of blood and iron status in respiratory disorders under the study. We are giving some brief about iron and ACD.

PATHOPHYSIOLOGY OF IRON METABOLISM :

Introduction to Iron :

The iron is one of the most important metal in body which forms haemoglobin to transport oxygen from lungs to peripheral tissues. The iron is vital not only for our living cells but also to the bacteria for survival and multiplication.

Total iron in body is 4 to 5 gm of which 65% is in haemoglobin and 30% is in storage form in body. About 1 to 1.5 mg iron is usually consumed orally and the same amount is expelled out daily.

Mechanism of absorption of iron and its regulation in body :

The oral iron reaches to enterocytes (duodenal cell) for absorption and on entering the cells a part remains in enterocytes as ferritin and the other goes out through ferroportin protein. This part combines with transferrin and through circulation reach to red cells in bone marrow. The enteric cells are shed off in every 3 to 4 days and ferritin iron pass out in feces. When iron is sufficient in body then hepcidin is formed by liver which block the ferroportin and thus iron absorption is stopped.

The excess of iron in body is deposited in body in the form of ferritin and haemosiderin. This is storage form of iron for any emergency. The ferritin is deposited in liver (750mg) hepatocytes, spleen and bone marrow. When ferritin storage is full then it is converted into haemosiderin and deposited in other tissues like pancreas, heart, adrenal glands, thyroid and parathyroid glands and skin in the form of haemosiderin. This process is known as haemochromatosis and its excess may cause organ failure.

PATHOPHYSIOLOGY OF ACD :

For our study on anaemia of chronic disorders the diseases we have included are pulmonary tuberculosis, COPD, pleural effu-

sion, pneumothorax, and pyothorax. These illnesses when present can cause anaemia.

- *The exact mechanism of ACD is not fully clear.*
- *It is known that a bacterial pathogen needs iron for its survival and multiplication. Therefore the overall effects of changes in the body is to cause sequestration of iron so that it may not be available freely to the bacteria.*
- *Whenever our body senses a potential threat of bacterial invasion the iron is taken up by macrophages and converted into ferritin. Only just enough iron is supplied to the bone marrow for red blood cells and surplus is not left for microbes.*
- *On entry of any bacterial pathogen due to inflammatory stress cytokine interleukin -6 is produced which in turn institute production of hepcidin by the liver. Both of these have their multiple actions at multiple sites.*
- *The hepcidin blocks the activity of ferroportin present in enterocytes, hepatocytes and macrophages. Due to this the iron is not absorbed into body and moreover it cannot be released from the hepatocytes and macrophages. The extra free iron being collected by macrophages and also by hepatocytes is converted into ferritin. As a result serum ferritin level rises.*
- *Secondly the hepcidin institute the phagocytosis of iron present anywhere by macrophages*
- *Therefore there is hypoferremia, so that iron is not available for new haemoglobin synthesis.*
- *The inflammatory cytokines reduce the ferroportin expression and also blunt the erythropoiesis by blunting the response of bone marrow to respond to the EPO.*
- *The EPO levels although are increased but it does not cause increase in erythropoiesis which may be perhaps due to death of red cell precursors.*
- *If the inflammation continues, the effect of locking up of iron is to reduce the ability of bone marrow to produce red cells. These red cells require lot of iron for producing massive amounts of haemoglobin which is used to transport oxygen from lungs to peripheral tissues.*
- *In a person with ACD there is decline in haemoglobin. The haemoglobin value may remain in the range of 9 to 10.5 gm/dl or below this level depending upon the type of infection. The anaemia is improved when the underlying disease is cured.*
- *The cytokines prevent the differentiation of stem cells into red cells and promote the production of WBC.*
- *A brief of the pathogenesis of ACD is as follows –*

❖ *The interleukin 6 is central mediator of anaemia of chronic disease. They influence hepcidin production by liver which cause reduced iron absorption and increased phagocytosis of iron by macrophages, and reduced production of erythropoietin and its blunting action on erythropoiesis.*

❖ *The hepcidin reduces release of iron from hepatocytes and macrophages by blocking the ferroportin present in their cell membrane.*

❖ *Therefore ACD is associated with hypoferremia.*

❖ *The interleukin 6 causes reduction of red cells by suppression of red cell precursors in bone marrow, reduces the life span of red cells, increases blood volume by which red cells in per unit area are decreased causing anaemia.*

- *Although the ACD can accompany a life threatening illness, but it is a protective and natural mechanism which our body adopts by limiting the available iron when harmful things like bacteria get into our body. We mean to say that all the living things including bacteria and our cells depend upon iron to sustain life. This theory was described by Eugene Weinberg, PhD, Indiana University in 1980.*
- *The anaemia of chronic illness is a indicator that some serious life threatening condition is in initial stage of development, therefore the patient needs thorough investigations.*

Investigation of a case of ACD patient :

❖ *History of blood loss from body and its source. Stool and urine examinations to know any occult blood to search any reason for it. These are relating to IDA.*

❖ *Complete haemogram which is of help in D/D of anaemia.*

❖ *Serum unconjugated bilirubin examination .*

❖ *Serum folic acid and B12 estimation .*

❖ *General Blood Picture (GBP) examination .*

❖ *Serum transferrin receptor examination is useful guide for iron deficiency or ACD. It is high in IDA and normal or low in ACD.*

❖ *Bone marrow examination .*

MATERIAL AND METHODS :

Study settings :

All the patients selected for the study were those who attended the out patient department of the pulmonary medicine in Rohilkhand medical college and hospital, Pilibhit bypass road at Bareilly. All the patients selected for the study were admitted in the department of pulmonary medicine at Rohilkhand medical college and hospital , Pilibhit by pass road Bareilly which is a tertiary care teaching hospital in Bareilly. This hospital is a big hospital with well equipped infrastructure and well trained human resources, having all the routine essential departments with the provision for post graduate studies in all of these departments. The duration for the study of the patients was from January 2014 to June 2015.

Aim of study :

Our aim is to study the specific features of anaemia of chronic disorders (ACD) like hypoferremia with high ferritin value. The study is aimed to prove the high ferritin value in ACD patients but the patients are being treated as a case of iron deficiency anaemia which is injurious for the patients due to the complication of iron overloading and resulting harms of haemochromatosis leading to organ failure .

Definition of anaemia:

We called patients anaemic when the haemoglobin in males was less than 13gm/dl, and less than 12 gm/dl. In females, as per WHO recommendations.

Plan of study of ACD patients :

Our study is in two parts as follows :

o *The first part of our study was done on 582 patients of respiratory infections. After screening 156 patients were excluded due the probability of any other associated irrelevant disorder and 426 patients of respiratory infections were selected who were having $PTB_{(163patients)}$, $COPD_{(190patients)}$, $Pleural\ effusion_{(36patients)}$, $Pyothorax_{(24patients)}$ and $pneumonia_{(13patients)}$. We found that in these 426 patients the 38 patients were not having anaemia and 388 patients were having anaemia. All these after preliminary screening were hospitalized. They were further investigated for haemoglobin level and for morphological feature of red cells like microcytic hypochromic or normocytic normochromic features by GBP examination. This is mainly to know the severity of anaemia. These 388 patients were carried forward to our second part of study .*

o *The other part of the study is done on 388 ACD patients (with 151PTB,+170 COPD,+32 Pl. Effusion,+23 Pyothorax, and +12 Pneumonia patients) + 20 new normal people (control) + 20 new patients of iron deficiency anaemia with total of 428 patients which were divided into 4 groups. The first group is of 20 normal (control) persons. The group second consists of PTB patients . The third group consists of COPD patients, Pleural effusion patients, Pyothorax patients and Pneumonia patients . The fourth group is of 20 new patients having iron deficiency anaemia only (not any chronic disorder disease) selected from the admitted patients in hospital. In this study we have studied about haemoglobin status, red cell indices, GBP status, and values of serum iron level, Transferrin saturation percentage, and serum ferritin level of each of these 428 patients.*

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Age and sex distribution of patients :

Table – 1 The age wise and sex wise distribution of 426 ACD patients,

Age Group of ACD patients	Sex	Pulmonary TB Pt. (% Out of 163 Pts.)	COPD Pt. (% Out of 190 Pts.)	Pleural effusion Pt. (% Out of 36 Pts.)	Pyothorax Pt. (% Out of 24 Pts.)	Pneumonia Pt. (% Out of 13 Pts)
15-30 yr	Male	36 (22%)	0	9 (25%)	3 (13%)	2 (15%)
	Female	18 (11%)	0	4 (11%)	3 (12%)	1 (8%)
31-45 yr	Male	28 (17%)	11 (6%)	7 (19%)	10 (42%)	2 (15%)
	Female	8 (5%)	10 (5%)	4 (11%)	2 (8%)	1 (8%)
46-60 yr	Male	44 (27%)	99 (52%)	6 (17%)	4 (17%)	2 (15%)
	Female	6 (4%)	22 (12%)	2 (6%)	2 (8%)	1 (8%)
Above 60 yr	Male	23 (14%)	42 (22%)	3 (8%)	0	4 (31%)
	Female	0	6 (3%)	1 (3%)	0	0
Total	Male 335(78%)	131 (80%)	152 (80%)	25 (69%)	17 (71%)	10 (77%)
	Female 91(22%)	32 (20%)	38 (20%)	11 (31%)	7 (29%)	3 (23%)
Gross total	426 Pts.	163 (38%)	190 (45%)	36 (8%)	24 (6%)	13 (3%)

Analysis of table 1 for age and sex distribution of 426 patients :

- *The patients are divided in 4 groups –15-30, 31-45, 46-60, and above 60 yrs.*
- *In all types of infections males are affected by around 70 to 80% and females by 20 -30%.*
- *The maximum no. of patients are in COPD , then in PTB , then in Pleural effusion , then in Pyothorax , then in Pneumonia .*

Table 2 Study on analysis of haemoglobin and GBP of 426 ACD patients

*Selected patients in groups (% out of total 426 patients) – PTB 163 (38%), COPD 190 (45%), Pleural Effusion 36 (8%), Pyothorax24 (6%), Pneumonia 13 (3%) = Total 426
*Patients with normal blood (% out of groups of patients) —PTB 12 (7%),COPD 20 (11%),Pl. Eff. 4 (11%), Pyothorax (14%), Pneumonia (18%)= Total 38(9% of 426)
*Balance 388 ACD patients for study (% out of 388 patients [426 – 38])-- PTB151(39%),COPD 170 (44%), Pl.Eff.32(8%), Pyothorax23(6%), Pneumonia12(3%)= Total 388

Disease Groups	Haemoglobin Level		Red cell morphology					
			Normocytic normochromic			Microcytic hypochromic		
	Above 10 gm	Below 10 gm	Hb above 10 gm	Hb below 10 gm	Total	Hb above 10 gm	Hb below 10 gm	Total
$PTB_{151Pt.}$	$37_{24\%}$	$114_{76\%}$	$19_{12\%}$	$15_{10\%}$	$34_{22\%}$	$18_{12\%}$	$99_{66\%}$	$117_{78\%}$
$COPD_{170Pt.}$	$140_{82\%}$	$30_{18\%}$	$135_{79\%}$	$20_{12\%}$	$155_{91\%}$	$5_{3\%}$	$10_{6\%}$	$15_{9\%}$
Pleural effusion$_{32Pt.}$	$25_{78\%}$	$7_{22\%}$	$21_{66\%}$	$4_{12\%}$	$25_{78\%}$	$4_{13\%}$	$3_{9\%}$	$7_{22\%}$
$Pyothorax_{23Pt.}$	$18_{78\%}$	$5_{22\%}$	$18_{78\%}$	$0_{0\%}$	$18_{78\%}$	$0_{0\%}$	$5_{22\%}$	$5_{22\%}$
$Pneumonia_{12Pt}$	$9_{75\%}$	$3_{25\%}$	$9_{75\%}$	$3_{25\%}$	$12_{100\%}$	$0_{0\%}$	$0_{0\%}$	$0_{0\%}$
Partial Total	$229_{59\%}$ of 388Pt	$159_{41\%}$ of 388 Pt	$202_{52\%}$	$42_{11\%}$	***244*** $_{63\%}$ *of 388 Pt*	$27_{7\%}$	$117_{30\%}$	***144*** $_{37\%}$ *of 388 Pt*
Gross total	388		244 + 144 = 388					

Analysis of table number 2 for results of haemoglobin and GBP features in ACD patients :

We have divided the ACD patients into two categories, the one having moderate anaemia (upto 10 gm Hb) and the other having severe grade anaemia (having less than 10 gm Hb). Each of these categories have been subdivided into having normocytic normochromic and microcytic hypochromic patients. The details of reports are as under –

- *Hb above 10 g in PTB is 24% , in COPD is 82% ,in Pleural effusion is 78% , in Pyothorax is 78% , in Pneumonia is 75% .*
- *Hb below 10 g in PTB is 76% , in COPD is 18% ,in Pleural effusion is 22% , in Pyothorax is 22% , in Pneumonia is 25% .*
- *Normocytic and normochromic anaemia in PTB is 22% , in COPD is 91% ,in Pleural effusion is 78% , in Pyothorax is 78% , in Pneumonia is 100% .*
- *Microcytic hypochromic anaemia in PTB is 78% , in COPD is 9% ,in Pleural effusion is 22% , in Pyothorax is 22% , in Pneumonia is 0% .*

Table No. 3 Results of haemoglobin level, red cell indices, GBP and serum iron levels : Total number of patients 428

	Total patients 428 $_{(20+151+170+32+23+12+20)}$			
Investigations	Control Normal people 20 people i	PTB 151 pts. Ii	COPD 170 Pts Pl. Effusion 32Pts Pyothorax 23Pts Pneumonia 12Pts iii	Iron deficiency Anaemia 20 pts. iv
The values of Invest. have been mentioned in range and not exact because they belong to groups of people				
Hb	12—13gm	>below 10gm	> above 10gm	Upto 5gm or less
Red cell count	>5 mil	Around 3 mil or less	Around 3 mil or less	Around 3 mil or less
MCV	>76 fl	>Reduced	>Normal	All Reduced
MCHC	>30 gm/dl	>Reduced	>Normal	All Reduced
GBP	Normal RBCs	> microcytic hypochromic	>Normocytic normochromic	All Microcytic Hypochromic

Serum Iron,	60-130 mcg Normal	Moderately Reduced in nearly 100%	Moderately reduced in nearly 100%	Severely Reduced
Transferrin saturation %	Normal 20 – 50 %	Less than 20% in 100% cases	Less than 20% in 100% cases	Less than 20% in 100% cases
Serum ferritin	Around 77 ng/ml Normal in 100% cases	Raised more than 300 ng/ml in 100% cases	Raised more than 300 ng/ml in 100% cases	Can Reduce to 15ng/ml Or even less
Serum iron normal is 50—150 mcg/dl iron bound with transferrin ; Transferrin saturation % normal 20 to 50 % ; S. ferritin (In S. ferritin value at 15ng/ml the iron store is 0, In S. ferritin value at 100ng/ml the iron store is 800 mg) Normal value of S. ferritin is 30 to 250 ng/ml.				

Analysis of Table 3 (Total 428 patients) :

- *From the Table no. 3 we infer the ferritin level in different categories of patients . We found the ferritin level is within normal range in cases of control group(20 persons) , ferritin level more than 300 ng/ml in 100% (388 patients) cases of PTB, COPD , Pl. Effusion , Pyothorax , Pneumonia and ferritin level is below 15 ng/ml in case of IDA (20 patients) .*

Diagnosis :

All the ACD patients were diagnosed by proper history, complaints, physical examination and relevant investigations.

Treatment of ACD patient :

- *Generally the ACD patients do not need any treatment for associated mild degree anaemia. These patients if treated for their cause of chronic illness, the anaemia will be automatically cured. In these cases the ferritin value is raised to normal value.*
- *Iron supplement should never be used either as I.V., or orally in association with vitamin tonics unless the iron deficiency has been proved by various baseline iron studies like serum ferritin which is low to very low. Adding of erythropoietin may help patients of this category in improving anaemia.*
- *The iron if given by I.V. route may become free in body and exposed to the utilization of microbes present in body which have caused the ACD.*
- *The blood transfusion must be given only to severely anemic patient when the patient is hanging between life and death. The problem in blood transfusion is that the iron of one bottle of blood is about 330 mg which after 120 days will later get deposited in various organs in the form of ferritin and haemosiderin causing haemochromatosis.*

Even in these patients the serum iron studies must be carried out.

- *To treat these ACD patients additionally the erythropoietin can be beneficial when given alongwith the treatment of chronic disorder.*
- *It is highly dangerous to give iron to any anemic patient of any etiology without investigating the iron status of patient. It is because we have found in our study that the ferritin levels are already raised to very high in ACD patients.*

Complications of iron overloading :

- *The complications of iron over loading in body are the following – cirrhosis of liver, hepatosplenomegaly, diabetes, congestive heart failure, arrhythmia, arthritis, costochondrosis, hypogonadism, hepatocellular carcinoma, loss of libido, spiders, jaundice, ascites and skin pigmentation. Ultimately organ failure is the result.*
- *The organs exposed for this kind of iron deposition are liver, spleen, kidney, heart, pancreas, pitutary, thyroid and adrenal glands, and skin. These organs are liable to be damaged and can cause various complications of which some may be fatal.*

Improvement in anaemia :

The improvement in anaemia after relevant treatment was defined when haemoglobin concentration was raised to more than 13gm /dl in males and 12gm/dl (WHO criteria) in females, by two times testing in 4 weeks apart.

Good clinical response :

This we define when after giving the treatment the patient feels better subjectively by expressing improvement in fever, anorexia, cough with expectoration and general well being. Additionally the haemoglobin is raised to near normal level gradually in 3 to 4 months time in about 75% of cases by treating the cause of disease. The care of rest of the patients is taken who also reach to about near normal values by proper nourished diet and proper treatment of the disease to which the patient is suffering. Care has to be taken that during therapy no iron supplement is given if not required and unless we are known of the iron status of the patient.

DISCUSSION :

It is a well known fact that all the living things including the bacteria and our cells depend upon iron to sustain life.

This is the reason whenever our body senses a potential threat of bacterial invasion the body defenses get activated to direct macrophages to take up iron and get it converted into its storage form, the so called ferritin. These macrophages do not release their iron to the bone marrow. Secondly the hepatocytes also do not release its iron for bone marrow. As a matter of fact the cell membranes of these macrophages and hepatocytes have ferroportin in their cell membrane through which only the iron can come out of it to be combined with the transferrin which supplies its iron to bone marrow during circulation. But the ferroportin is blocked by hepcidin in these conditions. Only just enough iron is supplied to the bone marrow for red cell formation and surplus is not left for microbes. Thus hypoferremia results in the presence of ample of iron in reticuloendothelial system.

As such it is clear that limiting the access of microbes to iron can limit the bacterial virulence and reduction of its multiplication due to which severity of infection is reduced although the anaemia appears as a side effect of our defense mechanism. But it cannot be denied that a sudden severe anaemia in the absence of iron deficiency is a alarm to search for any serious disease in the body. So in chronic diseases it advisable that Serrum ferritin test should be done to save patient from wrong diagnosis of anaemia .

Relation to age and sex :

In all ACD groups males are affected by 70 to 80% and females are affected by 20-30%. The peak of infection in females is 15 to 30 yrs. in PTB, 46 to 60 yrs. in COPD, and 15 to 45 years in pleural effusion.

Conclusion :

Anaemia is a common haematological abnormality with ACD . The anaemia can be mild , moderate or severe with mostly normocytic normochromic picture to microcytic hypochromic picture in few cases only . But microcytic hypochromic picture is a predominant feature in pulmonary tuberculosis secondly it is also to conclude that the serum ferritin value in almost all the ACD patients is above 300 ng/ml which indicates that iron is in increased amount in these patients and should be differentiated from IDA cases and be not treated on the line of IDA else if not properly examined it can lead to organ failure.

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