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Original Research Article

Iron profile in sickle cell heterozygous children: A case control study

Subas Chandra Majhi[1], Sameer Kiro[1], Mangal Charan Murmu[1], Pitambar Murmu[1], Shitanshu Kumar Meher[1], Sanjukta Panda[1], Himanshu Nayak[1]*

[1] *Dept. of Pediatrics, Veer Surendra Sai Institute of Medical Sciences and Research, Sambalpur, Odisha, India*

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ABSTRACT

Backgrounds: Iron deficiency is the most common nutritional deficiency worldwide & it is an important public health problem in developing countries like India. Normally chronic hemolytic anemia are iron loaded because of excessive breakdown of RBC & increased frequency of blood transfusion, but there is small or no transfusion on sickle cell trait. This study has been done to see the iron profile among sickle cell trait children in western Odisha.
Objectives: To determine the iron profile in children with sickle cell trait & normal healthy controls & compare them.
Materials and Methods: This was a case control study that has been conducted over a period of two years. A total of 202 subjects were included in the study; 102 of them were sickle cell heterozygous & 100 of them were normal healthy controls. Iron deficiency anemia among sickle cell trait & healthy controls were screened using various clinical & laboratory criteria.
Results: A total of 202(n=202) study populations comprising of 102 sickle cell trait & 100 normal study populations were screened. A little female preponderance (n=109, 54%) was observed in this study. Abnormalities in blood parameters like MCV, MCH, MCHC, Serum ferritin were found to be statistically significant ($p<0.005$). Others clinical features like pallor, picophagia, sore tongue, fatigue was also found to be statistically significant ($p<0.005$). Out of 202 study populations 17 out of 102 sickle cell trait cases & 16 out of 100 normal controls were found to have Iron deficiency anemia.
Conclusion: In this study it showed that there were many sickle cell trait patients who were actually iron deficient. These patients should be screened carefully to look for Iron deficiency anemia. Clinical parameters like pallor, fatigue, picophagia, sore tongue & others laboratories parameters like MCV, MCH, MCHC, Serum ferritin were helpful in diagnosing Iron deficiency anemia.

1. Introduction

The typical recurrence of sickle cell illness in India is 4.3% & in Orissa predominance is pretty much as high as 9.1%.[1] Lack of iron is the most widely recognized nourishing lack overall & a significant general medical condition particularly in non-industrial nations. There is no reasonable information about the number of people that are impacted by lack of iron around the world, yet it is assessed that ID is available in the greater part of the pre-younger students & pregnant ladies in agricultural nations & in no less than 30-40% in created nations when weakness is utilized as a circuitous sign of ID.[2] As per the 2001 World Health Organization (WHO) information, 30% of the youngsters matured somewhere in the range of 0 & 4 years & 48% of the kids matured somewhere in the range of 5 & 14 years are frail in creating countries2. In our country, the recurrence of iron lack frailty (IDA) has been accounted for

* *Corresponding author*.
E-mail address: nayakhimansu@gmail.com (H. Nayak).

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to run somewhere in the range of 15.2% & 62.5% in various examinations directed with youngsters.[3–5]

Extra reasons for sickliness in low-pay nations incorporate other healthful lacks (vitamin B12, folic corrosive, & riboflavin), ongoing illnesses, parasitic diseases like jungle fever, hemoglobinopathies, & lead poisoning.[6] Anemia is a huge reason for maternal passings & unfriendly pregnancy results in non-industrial nations. A new meta-examination showed that 42.7% of ladies in low-and center pay nations experienced pallor during pregnancy, & this was related with fundamentally higher dangers of low birth weight, preterm birth, perinatal & neonatal mortality. South Asian & African nations had the most elevated pooled paleness predominance. In general, 12% of low birth weight, 19% of preterm births, & 18% of perinatal mortality were owing to maternal anemia.[7]

Sickle cell illness was first portrayed by James B Herrick in 1910. It was very nearly forty years after the fact that Linus Pauling & his partners inferred that sickle cell infection was brought about by a hereditary problem. It is one of the notable atomic problems. It is called sub-atomic on the grounds that it is brought about by a solitary protein transformation. Sickle cell causes lifetime weakness from ongoing iron deficiency, organ harm prompting low quality of life, & early mortality. It is a significant general medical problem. Since the Sickle Cell Anemia Act laid out in 1972, there has been more evaluating for sickle cell quality & disease.[8]

Sickle cell characteristic is brought about by unusual hemoglobin called sickle hemoglobin or Hb S. Sickle hemoglobin is because of a point change in the beta globin chain. This point change replaces A with T at codon 6 of beta hemoglobin chain. This causes the change from glutamic corrosive to valine amino corrosive. The valine-type hemoglobin makes red cells sickle when presented to a low oxygen edge. Patient with sickle cell characteristic acquires HbS from one parent & HbA from the other parent making them heterozygous.

Sickle cell attribute is more predominant in individuals who are of African-plunge & furthermore whose progenitors come from tropical & sub-tropical districts where jungle fever is endemic. The predominance paces of sickle cell attribute in the United States is 9% among African American which is around 3 million individuals, & 0.2% among Caucasians.[9] Worldwide, it is assessed that there are 300 million individuals with sickle cell quality & 33% of this number are in sub-Saharan Africa.[10] The commonness of sickle cell characteristic is higher in regions where jungle fever is endemic. It is normally assumed that the patients with persistent hemolytic sickliness even of milder degree are iron stacked as a result of extreme breakdown of red platelet & periodic blood bonding.[11] This worry stops remedy of iron salts for sickle cell weakness & even sickle cell heterozygotes overall practice. The by & large clinical range of sickle cell characteristic makes their clinic visit less successive. In a situation in India where the pervasiveness of lack of iron is very high, even the heterozygotes are probably going to be iron inadequate.

In this guise, it is well-suited to have a logical knowledge into the iron profile of sickle cell heterozygotes in a geological area of high sickle cell quality weight. Subsequently the ongoing task proposition was embraced.

1.1. Research question

What is the iron profile in sickle cell trait children?

2. Aim

To study the iron profile of sickle cell trait in childhood age group.

3. Objective

To find out the iron profile among sickle cell trait children in the age group of 1 to 14 years & compare with normal healthy controls that are age & sex matched.

4. Materials and Methods

After getting clearance for institutional ethical committee the study was conducted at Veer Surendra Sai Institute of Medical Sciences & Research, Burla, Sambalpur from September 2019 to October 2021. The study settings were at the IPD & OPD of Department of Pediatrics & the Sickle Cell Institute of VIMSAR, Burla, Sambalpur. This was a case control study.

4.1. Study subjects

There were two group of subjects – case group & control group.

4.2. Inclusion criteria of cases

1. HPLC confirmed cases of sickle heterozygous children.
2. Age group from 1 to 14 years of either gender.

4.2.1. Inclusion criteria of controls

1. Apparently asymptomatic children with age group from 1 year to 14 years of age preferably from sibling or accompanying children OPD/IPD & Sickle cell clinic.
2. Children having normal HPLC report.

4.3. Exclusion criteria of cases & controls

1. History & documentation of consumption of iron in last 3 month

2. History & documentation of consumption of folic acid in last 3 month
3. History of blood transfusion in last 3 month
4. History of bleeding disorders
5. History of malignancy
6. History of chelation therapy
7. History of any inflammatory disease state

4.4. Estimation of minimum sample size

Based on a previous study done in India in 2005 by Balgir RS et al the prevalence of sickle cell trait was 6.4%7. The frequency of sickle cell trait among various age groups, which included young children, adults, & individuals over 65 years of age, ranged from 6.4% to 7.4%. Taking it into consideration & with an absolute precision of 5% & with 95% confidence interval the required sample size was calculated as 102 by Single Proportion Absolute Precision method.

The detailed calculation was as follows:

$n = Z^2PQ/d^2$

$= (1.96)^2 \times 6.4 \times (100-6.4)/5^2$

$= 92$

Where, n = Sample size,

P = Prevalence of risk factor

Q = 1-P

Z = Z statistic for a level of confidence (1.96),

d = precision

Applying absolute error of 5%, sample size comes to be 92.

Considering 10% non-responder, the size calculated is 92 + 9.2 = 102

Therefore, the final sample size is estimated at a minimum value of 102.

4.4.1. Sampling techniques

The subjects were enrolled out of the study population based on inclusion & exclusion criteria. Sickling patients & the healthy controls accompanying patients enrolled in my study were those who had come to OPD, Sickle cell clinic every day & all those sickling patients admitted to inpatient department of pediatrics.

4.5. Study tools & techniques

4.5.1. Automated high-performance liquid chromatography (HPLC)

It is done by the instrument "Variant β thalassemia short programme" supplied by Bio Rad laboratory. Main principle is the interchange of charged groups on the ion exchange material with charged groups on the hemoglobin molecule.

4.5.2. Complete blood count estimation

It was done by auto analyzer of trade name Sysmex XN1000.

4.5.3. Serum iron estimation

(Ferene-S method) Instrument used: SEAC CH-IOO (AMES, Miles India Ltd.).

4.5.4. Total iron binding capacity (TIBC)

(Ferene-S method) Instrument used: SEAC CH-IOO (AMES, Miles India Ltd.)

4.5.5. Serum transferrin estimation

(Immunoturbidometric method) (Instrument used: SEAC CH-IOO (AMES, Miles India Ltd.)

Serum ferritin estimation

The method principle for measurement of Ferritin is immuno-turbidimetry using Roche kits on the Hitachi 912 clinical analyzer.

4.5.6. Data collections methods

All the relevant data were collected in a predesigned case report format (CRF).

4.5.7. Data management

Data validation & data cleaning was done manually by two separate persons not involved in the study.

4.6. Data analysis

Continuous data were communicated in mean ± SD; straight out information were communicated in extents. Information predictability testing of nonstop information was finished by Shapiro Wilk's test and Greenhouse Geisser remedy was finished by Mauchly's test. All the engaging and inferential insights were finished by SPSS v 25 (IBM, New York). For all measurable purposes p esteem <0.05 was thought of as critical.

4.7. Perception

A sum of 202 subjects made up the review bunch. Of these guys were 93(46%) and 102 were females (54%), with M:F proportion of 0.85:1.The mean age among sickle cell characteristic was 10.12(±2.97) years where as mean age among ordinary review populace was 8.57(±2.93). The mean level among SCT was 131.44(±14.98) where as in typical populace it was 119.81(±17.69). In others factors like BMI, SCT and typical populace were 14.52(±1.59) and 14.84(±1.39) separately. The mean Hb among SCT was 10.10(±1.79) whereas in typical populace it was 9.75(±1.43). Additionally, others factors like MCV, MCH and MCHC it was observed that mean were somewhat on the higher side among Sickle Cell Trait as thought about ordinary review populace. Others variable like HbF, the mean among SCT was 1.52 (±0.57) though the mean among ordinary review population being 1.36(±0.47), which isn't just huge. The mean of Serum ferritin was on higher side among SCT when contrasted with ordinary populace for

example it is 89.82(±46.63) in SCT and 70.98(±43.87) in ordinary review populace. Essentially, among SCT the mean of Serum transferrin was 261.58(±68.83) while the mean among ordinary review population was 251.11(±70.27). There were not many factors like TIBC, the mean was viewed as on higher side among typical populace when contrasted with SCT, for example the mean was 346.02(±101.75) among typical review population while mean among SCT populace was 323.04(±104.53). There was no huge distinction between mean of serum iron among SCT and typical populace, for example 88.10 in SCT and 86.11 in typical review populace. Out of 202 subjects 33 were analyzed to have lack of iron paleness with aggregate level of 16.3%. The different consistent and clear cut factors are portrayed underneath.

Table 1 shows the clinical characteristics of study population in relation to Iron deficiencyanemia. Various variables like Height, MCV, MCH, MCHC, Fetal Hemoglobin, Sickled Hemoglobin, Serum ferritin were related significantly with Iron deficiency anemia. Others variables such as Weight, BMI, Hemoglobin were not as significantly related but they are statistically significant.

Variables such as Pallor, Fatigue, Picophagia, Sore tongue, Worm infestation have been taken into consideration against SCT children & normal children. Various categorical variables such as pallor & picophagia were found to be statistically significant in both the groups where as others variables like fatigue, sore tongue & worm infestation were found to be statistically insignificant.

Out of 202 study populations there were 33 children having IDA, out of which 17 belongs to SCT groups whereas 16 belong to healthy control with a cumulative percentage of 16.3%.Table 4

Association of pallor between iron deficiency anemia of sickle cell trait versus normal children was statistically significant (Pearson chi-square 8.81; OR 0.44; 95% CI 0.36, 5.36; $p < 0.001$). There was 56% less odds of pallor among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anaemia of normal children.Table 5

Association of fatigue between iron deficiency anemia of sickle cell trait versus normal children was statistically insignificant (Pearson chi-square 0.03; OR 0.88; 95% CI 0.22, 3.48; $p > 0.05$). There was 12% less odds of fatigue among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children.Table 6

Association of picophagia between iron deficiency anemia of sickle cell trait versus normal children was statistically significant (Pearson chi-square 4.93; OR 0.10; 95% CI 0.01, 0.99; $p < 0.05$). There was 90% less odds of picophagia among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children.Table 7

Association of sore tongue between iron deficiency anemia of sickle cell trait versus normal children was statistically insignificant (Pearson chi-square 0.11; OR 1.33; 95% CI 0.24, 7.17; $p > 0.05$). There were 33% higher odds of sore tongue among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children.Table 8

Association of worm infestation between iron deficiency anemia of sickle cell trait versus normal children was statistically insignificant (Pearson chi-square 0.43; OR 0.44; 95% CI 0.03, 5.35; $p > 0.05$). There was 56% less odds of worm infestation among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children.Table 9

5. Discussion

In the present study; Group A consisted of 102 subjects consisting of HPLC confirmed cases where as Group B consisted of 100 normal study populations. A little female preponderance was observed in this study [males 93/202 (46%)]. Srinivas Other authors have also observed similar findings in their study.[13–15]

Among subjects in both the groups 33 were found to have Iron deficiency Anemias based on clinical features & various blood parameters like Hb, MCV, MCH, MCHC, Serum Iron, Serum Ferritin, TIBC. In SCT group 17(16.6%) subjects had iron deficiency anaemia. In healthy control group 16 (16%) children were diagnosed with iron deficiency anaemia.

Consequences of the ebb and flow concentrate on reports a higher commonness when contrasted with the concentrate by Patra et al[12] and Okeahialam and Obi[16] who tracked down lack of iron in 6% and 7.76% instances of sickle cell illness separately. Notwithstanding, iron lack was analyzed by Kassim et al[17] involving comparable standards in Yemini patients in 13.3% and by Vichinsky et al[18] in 16% of patients of sickle cell illness. There are no reports accessible as respect the pervasiveness of lack of iron weakness in sickle quality youngsters accordingly. This variety might be attributable to various review populaces or geographic variety and natural elements and can likewise be made sense of based on contrast between Western and Indian dietary propensities.

In our review the mean patients' serum ferritin (89.82 ± 46.44 ng/mL) was higher and likewise genuinely essentially ($p=0.003$) higher when contrasted and the mean serum ferritin of the controls (70.98 ± 43.87 ng/mL) which was inside the reference range. These discoveries in the patients showing expansion in body iron stores are with regards to Peterson et al. who detailed a high mean serum ferritin in a companion of cases which included kids determined to have both sickle cell quality and sickle cell frailty contrasted with the control.[19]

Table 1: Base line characteristics of continuous variables

Variables	Groups	
	Sickle Cell Trait Mean (SD)	Normal Mean (SD)
Weight of The Children in Kg	26.72 (7.83)	27.50 (17.55)
Height of The Children in cm	131.44 (14.98)	119.81 (17.70)
BMI in Kg/m2	14.52 (1.59)	14.84 (1.40)
Hemoglobin in gm/dl	10.10 (1.71)	9.75 (1.44)
Sickle Hemoglobin (HBS) in %	40.87 (9.69)	0.00 (.00)
Mean Corpuscular Volume [MCV] in fl	82.22 (6.32)	79.89 (5.50)
Fetal Hemoglobin (HBF) in %	1.52 (.58)	1.36 (.48)
Mean Corpuscular Hemoglobin [MCH] in pg/cell	28.96 (1.95)	28.24 (2.33)
Mean Corpuscular Hemoglobin Concentration [MCHC] in gm/dl	31.96 (2.10)	30.29 (2.04)
Serum Ferritin in ng/dl	89.82 (46.64)	70.98 (43.87)
Serum Iron in μg/dl	88.10 (26.98)	86.11 (31.35)
Serum Transferrin in μg/dl	261.58 (68.84)	251.11 (70.28)
Serum Total Iron Binding Capacity in μg/dl	323.04 (101.75)	346.02 (104.53)

Table 2: Baseline characteristics of categorical variables

Variable		SCT Group (n=102)	Normal Group (n=100)	Chi-Square	Odds Ratio	95%CI		p-value
						Lower Limit	Upper Limit	
Pallor	Yes	3	14	8.81	5.37	1.49	19.32	0.005
	No	99	86					
Fatigue	Yes	8	11	0.59	1.45	0.55	3.77	0.44
	No	94	89					
Picophagia	Yes	1	7	4.8	7.60	0.92	62.96	0.034
	No	101	93					
Sore Tongue	Yes	4	3	0.128	0.76	0.16	3.47	1.0
	No	98	97					
Worm Infestation	Yes	1	3	1.06	3.12	.31	30.54	0.36
	No	101	97					

Table 3: Independent 't test' of study variables in sickle cell trait as compared to healthy control

Variables	t-value	df*	p-value
Weight (Kg)	0.64	200	0.52
Height (cm)	5.05	200	0.000**
BMI (Kg/m^2)	-1.52	200	0.13
Hemoglobin	1.69	200	0.11
Sickle cell hemoglobin (HbS in %)	42.16	200	0.000**
MCV (fl)	2.79	200	0.006**
Fetal hemoglobin (HbF in %)	2.13	200	0.034**
MCH (pg/cell)	2.40	200	0.017**
MCHC (gm/dl)	5.37	200	0.000**
S. Ferritin (ng/dl)	2.96	200	0.003**
S. Iron (μg/dl)	0.48	200	0.63
S. Transferrin (μg/dl)	1.07	200	0.28
S. TIBC (μg/dl)	-1.58	200	0.115

*df- degree of freedom;
**p value <0.05 is considered statistically significant.

Table 4: Prevalence of IDA in both study groups

Study Groups	IDA Present	IDA Absent	% IDA
SCT(n=102)	17	85	16.6%
Healthy control(n=100)	16	84	16%

Table 5: Association of pallor with iron deficiency anaemia in both groups

Subgroup [n]	No of subjects with Pallor	Chi Square Value	Odds Ratio	95%CI		p Value
				Lower Limit	Upper Limit	
SCT with IDA [12]	3	8.81	0.44	0.36	5.36	**<0.001**
Control with IDA [13]	11					

Table 6: Association of fatigue with iron deficiency anemia in both groups

Subgroup [n]	No of subjects with fatigue	Chi Square Value	Odds Ratio	95%CI		p Value
				Lower Limit	Upper Limit	
SCT with IDA [12]	6	0.03	0.88	0.22	3.48	>0.05
Control with IDA [13]	8					

Table 7: Association of picophagia with iron deficiency anaemia in both groups

Subgroup [n]	No of subjects with picophagia	Chi Square Value	Odds Ratio	95%CI		p Value
				Lower Limit	Upper Limit	
SCT with IDA [12]	1	4.93	0.10	0.01	0.99	**<0.05**
Control with IDA [13]	6					

Table 8: Association of sore tongue with iron deficiency anaemia in both groups

Subgroup [n]	No of subjects with sore tongue	Chi Square Value	Odds Ratio	95%CI		p Value
				Lower Limit	Upper Limit	
SCT with IDA [12]	4	0.11	1.33	0.24	7.17	>0.05
Control with IDA [13]	3					

Table 9: Association of worm infestation with iron deficiency anaemia in both groups

Subgroup [n]	No of subjects with sore tongue	Chi Square Value	Odds Ratio	95%CI		p Value
				Lower Limit	Upper Limit	
SCT with IDA [12]	4	0.43	0.44	0.03	5.35	>0.05
Control with IDA [13]	3					

The mean MCV acquired in this study was higher than the qualities revealed for sound people for example mean MCV is (82.22±6.32) in SCT while in solid controls it was (79.89±5.80). This outcome is in concurrence with the mean MCV was accounted for to be equivalent to the qualities acquired in sound people by Khan et al [20] (89.4±8.7 fL) in India, El Ariss et al [21] in Lebanon (84.3±7.6 fL).

One youngster had history of worm pervasion for the situation bunch while there were 2 cases in the benchmark group. In our review relationship between lack of iron paleness and worm pervasion is genuinely immaterial as portrayed by Pearson Chi-Square worth of 0.43, p>0.05. There was 56% less chances of worm pervasion among lack of iron frailty of sickle cell attribute youngsters when contrasted with that of lack of iron sickliness of ordinary kids. This might be conceivably because of better well being training and its effect on way of life. There was a comparable report done by Das P K et al [22] in Odisha where they have tracked down that hunger and worm pervasion as the commonest cause behind lack of iron weakness in offspring of Sickle cell illness and Sickle cell characteristic.

There were 4 cases and 3 controls that were distinguished to have sore tongue. In our review relationship between lack of iron frailty and sore tongue is genuinely huge. There were 33% higher chances of sore tongue among lack of iron paleness of sickle cell attribute kids when contrasted with that of lack of iron weakness of ordinary youngsters. A comparative assertion was made by Porter SR et al, [23] which was upheld by JS Renne et al. [24] He referenced in his review that negative iron equilibrium prompted exhausted iron stores which caused epithelial decay. As indicated by his review, oral ulcerations were the most well-known infection which was brought about by epithelial decay brought about by lack of iron.

In both the groups there were 7 children with picophagia with one in the case group. Association of picophagia

between iron deficiency anemia of sickle cell trait versus normal children was statistically significant. There was 90% less odds of picophagia among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children. The characteristic may be explained by better health education opportunities in the case group with a higher frequency contacts with heath care providers facilitating better yield in BCC-behaviour change communication. Similar study done by Borgna-Pignatti et al showing significant relationship between picophagia & Iron deficiency anaemia in children between 2 to 7 years of age of which most of them are belong to low socio-economic status.[25]

There were 14 children having pallor; 3 were amongst cases with iron deficiency & the rest in those without iron deficiency. In the control group among those with iron deficiency anaemia 11 had pallor. Association of pallor between iron deficiency anemia of sickle cell trait versus normal children was statistically significant. There was 56% less odds of pallor among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children. The finding may be explained by the higher mean hemoglobin in the case group as compared to the healthy control group. Similar study done by Aggarwal et al in 2014 showing significant association of pallor in diagnosing anaemia in children between 6 months to 5 years of age.[26]

In our study group, there were 16 children having fatigue out of which 8 were belong to Sickle cell trait group. Association of fatigue between iron deficiency anemia of sickle cell trait versus normal children was statistically insignificant. There was 12% less odds of fatigue among iron deficiency anemia of sickle cell trait children as compared to that of iron deficiency anemia of normal children. This can also be ascribed to a higher mean hemoglobin level in the group.There is also similar study done by Paoletti G et al in 2014 showing that Iron deficiency anaemia was significantly associated with fatigue as well as pallor.[27]

6. Limitations of the study

This study included a selected small number of cases. A multicentric study involving a greater number of patients should be carried out to generalizing the finding of this study.

7. Conclusion

Iron deficiency is a clinical problem, though the commonest cause of anaemia all over the world is supposed to be absent in hemolytic anaemia with contraindication of iron therapy. But the iron status in sickle cell trait has never been accurately assessed especially in children.

The prevalence of iron deficiency is equal & comparable between those children with sickle cell trait & the healthy counterparts in a developing country scenario. There are minor but significant atypicality to the common signs & symptoms detected with the condition in sickle trait like less association of pallor, sore tongue, worm infestation & picophagia but higher association of fatigue. Hence Sickle cell trait children must be screened routinely for iron deficiency. Judicious Iron therapy should be instituted to all detected iron deficient cases.

8. Author's Contribution

1. Subas Chandra Majhi: Study concept, Research design
2. Pitambara Murmu: Literature, Data collection
3. Himansu Nayak:Data compilation, Method
4. Sameer Kiro: Data analysis, Method
5. Sitanshu Kumar Meher: Method, design
6. Mangal Charan Murmu: Manuscript preparation & Editing, Coordination

9. Conflict of Interest

The authors do not have any conflicts of interest.

10. Source of Funding

None.

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Author biography

Subas Chandra Majhi, Associate Professor

Sameer Kiro, Assistant Professor

Mangal Charan Murmu, Associate Professor https://orcid.org/0000-0003-2606-6545

Pitambar Murmu, Resident

Shitanshu Kumar Meher, Associate Professor

Sanjukta Panda, Associate Professor

Himanshu Nayak, Assistant Professor

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