A SYSTEMIC REVIEW OF FREQUENCY AND MANAGEMENT OF DIFFERENT TYPES OF ANEMIA IN RURAL AREAS OF NORTHERN PUNJAB, PAKISTAN: A CROSS SECTIONAL STUDY

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ABSTRACT

The present cohort study was conducted on a total of 592 patients including those hospitalized after being operated as well as those who visited the hospital with symptoms of anemia. These patients were reviewed for demographic data such as age, sex, clinical features and socioeconomic status, results of laboratory tests and for the underlying causes of their symptoms of anemia in DHQ hospital Jauharabad, THQ hospital Nurpur, THQ hospital Quaidabad and THQ hospital Naushehra. Among the patients included in the study 213 were male and 379were female. The most common age group was 21-30 years. The average hemoglobin was 8.5gm/dl, the lowest being 4.7gm/dl. Anemia due to decreased red cell production was found in 571 patients, anemia due to increased red cell destruction was found in 5 patients and anemia due to blood loss was found in 284patients.Anemia due to decreased red cell production was the most prevalent type of anemia in all age groups. The pattern of abnormalities in laboratory readings of anemic patients indicated that iron deficiency was the major cause of anemia in children, adolescents and adults whereas chronic disease was the leading cause in the elderly patients.

Keywords: Anemia, iron-deficiency anemia, causes of anemia.

INTRODUCTION

Anemia is a decrease in whole body red cell mass that precludes relative decreases in red blood cell count, hemoglobin or hematocrit, which occur when the plasma volume is increased[1]. Hemoglobin is an iron rich protein that carries oxygen from lungs to all body tissues. Thus due to decreased hemoglobin concentration, body organs do not receive enough oxygen.

Anemia is not a disease but rather a clinical feature of some other underlying problems that leads to hypoxia and a wide range of clinical consequences [2]. Anemia can be classified either by kinetic approach marked by production of RBCs, destruction of RBCs and by blood loss or by morphologic approach marked by RBCs size. RBCs sizes are classified as microcytic, if the cells are smaller in size than normal (under 80 fl), normocytic, if they have normal size (80-100 fl) and macrocytic, if they have larger size than normal (over 100 fl) [3, 4].

Causes of anemia can largely be categorized as anemia due to decreased RBCs production, anemia due to increased RBCs destruction and anemia due to loss of blood [5]. Decreased RBCs production can be attributed to decreased nutritional intake or decreased absorption of nutrients required for RBCs production i.e. folic acid, iron and vitamin B_{12}. Also chronic diseases including chronic liver disease, hypothyroidism or chronic infections can lead to

bone marrow depression. Other factors causing decreased RBCs production include conditions like myeloma and leukemia whereas cytotoxic drugs also lead to bone marrow suppression [5].

Increased RBCs destruction can be attributed to conditions like thalassemia, sickle cell anemia, leukemia, systemic lupus erythematosus and enzymopathies. Also hemolysis alongwith valvular heart disease results in RBCs destruction [5]. Anemia due to blood loss can be attributed to conditions like trauma, menorrhagia, hemorrhage, recurrent blood donation, operative blood loss, peptic ulcer and erosions [5].

In case of prevalence of anemia, anemia due to decreased production of RBCs is the most prevalent type of anemia. Iron deficiency anemia is found mostly in children, adolescents and adults whereas chronic disease is the major cause of anemia in elderly patients. Main causes of iron deficiency anemia include poor intake of diet and excessive blood loss. Children are mostly fed with cow's milk that is unable to fulfill their dietary iron requirements. It also hinders the absorption of iron from other foods, by the body. Mostly poor diet and insufficient iron intake to supplement menstrual loss or loss associated with diseases leads to anemia in adolescents and adults [6].Also hookworm infestation is the most common cause of prevalence of iron deficiency anemia in children as well as adolescents and adults [3]. In the developed world, the prevalence of iron deficiency anemia has definitely reduced because of improved nutrition, small family sizes, and routine prescription of prophylactic iron to every pregnant woman. In case of elderly patients, chronic disease affects the body's ability to produce red blood cells that ultimately leads to anemia.

Anemia can be treated by nutrients including vitamin $B_{12,}$ folic acid or ferrous sulphate in case of nutritional anemia. Also recombinant erythropoietin can be administered to treat anemia which can easily stimulate RBCs reproduction. But severe anemic cases require blood transfusion as well [7].

Anemic conditions can be managed but firstly its cause should be identified which can then be reversed. Hematinics administration for longer period of time can be inappropriate and result in surplus iron level whereas RBCs transfusion is also not the ultimate solution. That is why etiology should be identified for proper treatment.

Methodology

This cohort study was conducted in the District Headquarter hospital of Jauharabad and Tehsil Headquarter Hospitals of Naushehra, Nurpur and Quaidabad. All anemic patients of varied age, sex and socioeconomic status, hospitalized after some surgery or those who visited the hospital with symptoms of anemia were included in the study. Data was collected on a questionnaire proforma that was designed to contain two categories. One category comprised of questions that were to be asked from all patients while the other category comprised of questions that were to be asked from selected patients only.

First category included questions regarding age, gender, socioeconomic status, habitat, personal hygiene, history of dietary intake, history of blood in vomiting, history of blood in urine or stools, history of worm infestation, history of liver or kidney disease, surgical history, history of chronic disease, history of recurrent infections and history of weight loss or anorexia whereas the second category consisted of questions regarding history of frequent

blood donation, history of piles and in case of females it consisted of questions regarding no. of pregnancies and history of bleeding during menstrual cycle and child birth.

The diagnosis and causes of anemia were confirmed on the basis of physical examination and results of the laboratory tests. During physical examination, physician checked the heart rate of the patient, breath of the patient, skin and mucous membrane of the patient for pallor, jaundice, smooth or beefy tongue or koilonychias, abdomen for hepatomegaly and splenomegaly and some other signs that are often made worse by the anemia, such as worsening cognitive impairment, apathy, congestive heart failure and dizziness. Blood tests were recommended by the practitioner in order to measure the patient's red blood count and levels of hemoglobin. Hematocrit (red blood cell count) values of adults should be between 32% and 43%, whereas hemoglobin values should be from 11 to 15 grams per deciliter [8]. Those having lesser values than normal, have anemia. The blood tests also revealed the unusual shape, colour or size of the red blood cells. Patients with iron deficiency anemia (type of microcytic anemia) had paler and smaller red blood cells as compared to those in healthy individuals. Patients with vitamin deficiency (type of macrocytic anemia) had red blood cells, fewer in number and larger in size [8] while patients with normocytic anemia had red blood cells of normal size and fewer in numbers.

Treatment of anemia was not the same for all patients. It varied widely depending on the severity and cause of anemia. In case of anemia, related to low iron levels in the body, iron supplements were prescribed mostly. In patients with pernicious anemia, vitamin B_{12} levels were repleted in the body by using monthly injections of vitamin B_{12}. Blood transfusion was carried out in case of patients having congenital hemolytic anemia and sudden blood loss resulting from trauma and antepartum hemorrhage in order to relieve the symptoms of anemia and replace the lost blood. Blood transfusion was also recommended in some other less critical circumstances. For example, in case of cancer patients, who were receiving chemotherapy [9]. Erythropoietin was prescribed in case of patients with chronic diseases.

Statistical Analysis

Data was analyzed and calculations were made using Microsoft Excel Spreadsheets, Graphpad Prism 5.

Results

During the study period, data of 592 anemic patients was collected. Among the patients under study, there were 213 male patients and 379female patients (Figure 1).The mean age of patients irrespective of sex was 26 years, ranging from the age of neonatals to the age of 70 years. The average hemoglobin value was 8.5gm/dl whereas the lowest hemoglobin value was 4.7gm/dl. The ratio of male to female patients was 1:1.77, thus showing that anemia is more prevalent in females as compared to males. Average hemoglobin value tended to be lower in elderly people as compared to that in adults. The average hemoglobin value in elderly people was 7.5gm/dl whereas in case of adults, it was 8.3gm/dl.

As shown in Table 1, anemia due to decreased red cell production was found in 571 patients, anemia due to increased red cell destruction was found in 5 patients and anemia due to blood loss was found in 284 patients. In case of anemia due to decreased red cell production, nutritional anemia was found to be the leading cause of anemia as it was found in 546 patients. In case of nutritional anemia, iron deficiency anemia was found in 545 patients and

pernicious anemia was found in 1 patient only. Iron deficiency anemia due to poor dietary intake was found in 261 patients whereas that produced due to blood loss was found in 284 patients. Anemia due to chronic disease was found to be the cause of anemia in 22 patients, leukemia was the cause of anemia in 3 patients and anemia due to bone marrow suppression was found in none of the patients. In case of anemia due to increased red cell destruction, congenital hemolytic anemia and acquired hemolytic anemia were found in 5 patients. In case of congenital hemolytic anemia, thalassemia was found in 1 patient, systemic lupus erythematosus was also found in only 1 patient whereas spherocytosis and sickle cell anemia were found in none of the patients. In case of acquired hemolytic anemia, hemolytic disease of newborn was found in 3 patients. In case of anemia due to blood loss, trauma was the cause of anemia in 9 patients, operative blood loss was the cause of anemia in case of 33 patients (blood loss due to child birth was found in 24 patients whereas blood loss due to surgery was found in 9 patients), blood loss from GI tract was the cause in 21 patients, menorrhagia was the cause in 24 patients, antepartum hemorrhage in 5 patients, excessive no. of pregnancies in 60 patients, hookworm infestation in 72 patients, frequent blood donation in 48 patients and postpartum hemorrhage in none of the patients.

Table 1. Description of Anemic Cases

Type of anemia	No. of cases
A. Anemia due to decreased RBCs production	571
1.Nutritional anemia	546
a. Iron deficiency anemia	545
i. Iron deficiency anemia due to poor dietary intake	261
ii. Iron deficiency anemia due to blood loss	284
b. Pernicious anemia	1
2.Anemia due to chronic disease	22
3.Anemia due bone marrow suppression	0
4.Anemia due to leukemia	3
B. Anemia due to increased RBCs destruction	5
1.Congenital anemia	2
a. Thalassemia	1
b. Systemic lupus erythematosus	1
c. Spherocytosis	0
d. Sickle cell anemia	0
2.Acquired anemia	3
a. Hemolytic of newborn	3
C. Anemia due to blood loss	284
1.Blood loss in trauma	9
2.Operative blood loss	33
a. Blood loss due to child birth	24
b. Blood loss due to surgery	9
3.Blood loss due to GI bleeding	21
4.Blood loss due to hemorrhoids	12
5.Blood loss due to menorrhagia	24
6.Blood loss due to antepartum hemorrhage	5

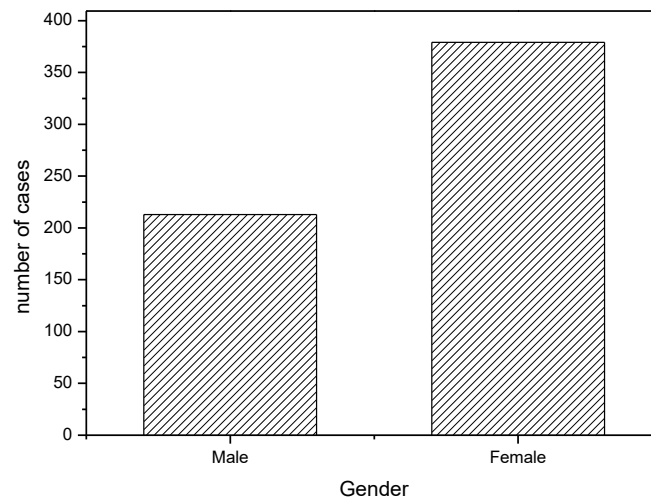| 7.Blood loss due to frequent blood donation	48
8.Blood loss due to excessive no. of pregnancies	60
9.Blood loss due to hookworm infestation	72

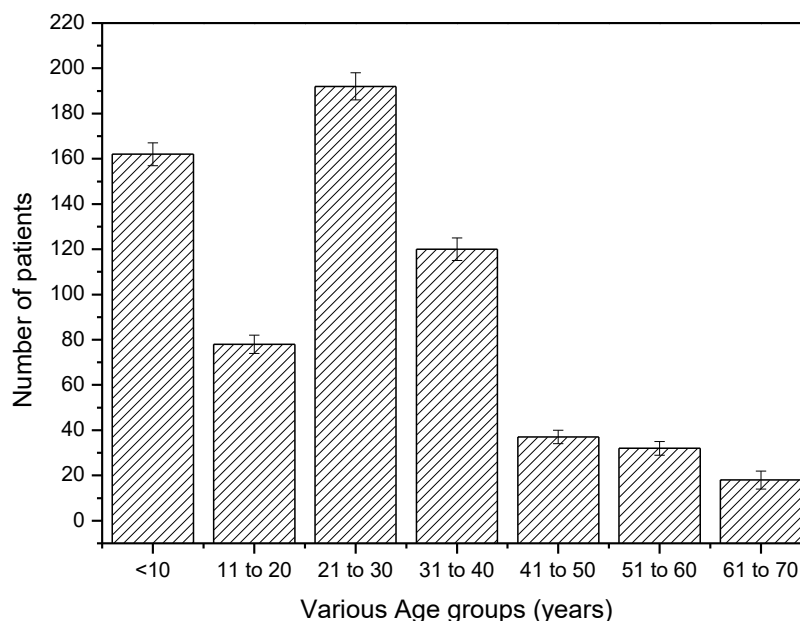Figure 1: Prevalence of anemia in male and female patients under study

Figure 2: Prevalence of anemia in different age groups under study

DISCUSSION

Amongst the types of anemia, iron deficiency anemia (type of nutritional anemia) was most prevalent in females [10]. The reasons behind increased prevalence of iron deficiency anemia in females were poor dietary intake and blood loss during menorrhagia, child birth, excessive no. of pregnancies, ante partum hemorrhage and hookworm infestation [10]. In developing countries, the incidence of iron deficiency anemia is high due to poor availability of good nutrition, large family sizes and no regular prophylactic iron therapy in pregnant women [10].

Among the pregnant women who visited the hospital, majority craved mud during pregnancy that led to increased hookworm infestation in them [3]. Hookworms cause anemia by ingesting blood from the intestine, by rupturing erythrocytes and by hemoglobin degradation in the host. In order to treat the hookworm infestation doctors prescribed a single dose of albendazole 400mg or mebendazole 100mg daily for three days, to the patients [11]. Adolescent female patients had a common complaint of having menorrhagia. Inspite of having menorrhagia, these patients were not taking iron supplements to fulfill the blood loss as they were not prescribed before. Doctors advised these patients to improve the quality of food in their daily diet and prescribed oral preparations containing ferrous sulfate or ferrous fumarate. Blood loss due to child birth and excessive no. of pregnancies, resulted in anemia in a small number of patients under study. In case of sudden blood loss due to child birth, blood transfusion was carried out firstly. Later the patients were advised to take oral or injectable iron and to improve their diet, in case of long term treatment [12]. In patients with excessive no. of pregnancies, anemia is developed due to blood loss, resulting from repeated deliveries. Thus the patients with history of excessive no. of pregnancies were advised to take iron supplements and to improve their diet. Antepartum hemorrhage is the vaginal bleeding occurring from 24 weeks gestation to the end of pregnancy [13]. Bleeding occurring during first and second stages of labor is also included in antepartum hemorrhage. Antepartum hemorrhage occurs with an incidence of 3.5% of all pregnancies. Anemia due to antepartum hemorrhage is treated by blood transfusion [13]. Thus blood transfusion was carried out for the patients, included in the study, who had anemia due to antepartum hemorrhage.

The major reasons behind lower average hemoglobin value in elderly patients were chronic diseases, malnutrition and poor hygiene. Chronic diseases that were mostly found in elderly patients included diabetes mellitus, hepatitis, cancer and rheumatoid arthritis. In case of diabetes mellitus, it is often associated with development of a complication including kidney damage ranging from diabetic nephropathy to chronic kidney disease as described earlier [14].
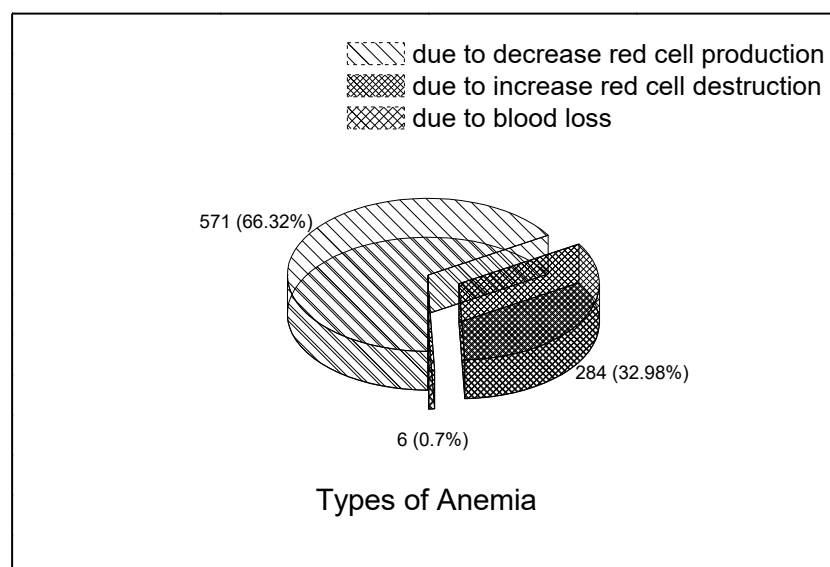
Hormone responsible for the production of red blood cells, erythropoietin, is produced by the kidneys. Thus kidney damage with diabetes results in anemia. Elderly patients having anemia due to diabetes were either treated with iron supplementation or with genetically engineered form of erythropoietin that was injected under the skin two to three times a week. In addition they were advised by the doctor to maintain their glucose levels at the target levels and to maintain their blood pressure under 130/80mmHg. They were also advised to control their lipids and to eat well balanced diet, comprising of foods that contain iron. In patients having anemia due to chronic hepatitis C, anemia develops either due to interference of the disease, as in the case of liver cirrhosis associated with hepatitis C or due to interference of treatment of the disease, with production of red blood cells. Anemia mostly begins soon after the initiation of ribavirin/ peginterferon therapy in the treatment of hepatitis C virus infection [15].
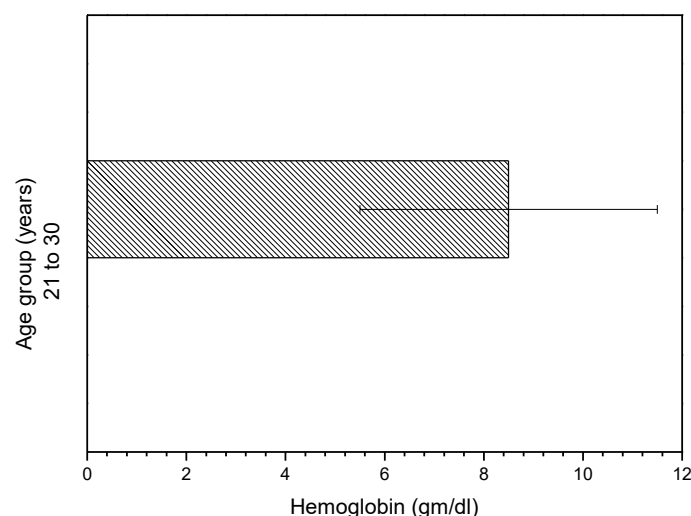
This anemia is then treated by reducing the dose of medication, by temporarily or permanently discontinuing ribavirin or by administering erythropoietin. Dose reduction or ribavirin discontinuation may affect the treatment efficacy therefore erythropoietin administration is the most preferred treatment for anemia inpatients with chronic hepatitis C [15].

In case of the elderly patients under study, who presented with symptoms of anemia with hepatitis C, recombinant human erythropoietin was prescribed. In case of cancer, it can give rise to anemia either due to direct effects of cancer cells on the body or due to the effects of biologically active products of cancer cells or as a consequence of the treatment of cancer. Cancer related anemia is treated after the cause of anemia is known. In case of the bleeding tumor of the bowel, it gives rise to iron deficiency anemia. This iron deficiency anemia can be cured by iron supplements but preferred treatment includes removal of the bowel cancer. When directly curable cause of anemia is not known, blood transfusion and erythropoietin therapy are preferred as discussed earlier [16].

In case of the cancer patients included in the study, patients with known cause of cancer were referred to an oncologist whereas in case of those with an unknown cause, blood transfusion and erythropoietin therapy were prescribed. Anemia due to rheumatoid arthritis is produced due to inflammation that occurs throughout the body. Proteins are released in the inflamed tissues of the body that affect the body's ability to use iron and produce RBCs. This ultimately leads to low red blood cell count [17].

Medication used to treat rheumatoid arthritis that includes NSAIDs and steroids mostly, may also be responsible for the development of anemia in most patients. These drugs can cause GI bleeding that may result in anemia, if not treated for a long time. Injectable erythropoietin or iron therapy are often beneficial for patients with anemia due to rheumatoid arthritis. Thus iron therapy was mostly prescribed by the doctor for the patients of anemia due to rheumatoid arthritis.

Types of Anemia

due to decrease red cell production
due to increase red cell destruction
due to blood loss

571 (66.32%)
284 (32.98%)
6 (0.7%)

In case of anemia due to decreased production of RBCs, nutritional anemia was the most common type of anemia found in the patients under study. It is mostly caused by lack of specific substances like iron, folic acid and vitamin B12, required for the synthesis of normal hemoglobin and erythrocytic maturation. It arises by several means, such as malabsorption or poor dietary intake. Iron deficiency anemia was produced due to diet, poor in iron and excessive blood loss whereas pernicious anemia was produced due to malabsorption of vitamin B_{12} [18]. Patients with iron deficiency anemia were treated either with oral iron or with parenteral iron. Blood transfusion or treatment of associated problems was also carried out, when required. In case of oral treatment, preparations containing ferrous sulfate or ferrous fumarate were prescribed to the patients. In patients showing poor compliance or tolerance to oral iron, parenteral iron was administered. Total dose of iron required for parenteral administration is calculated by using the following formula:

Elemental iron needed (mg) = (Normal hemoglobin-Patient's hemoglobin) × weight (kg) × 2.21 + 1000 [19].

Anemia of chronic disease was the major cause of anemia in elderly patients. Leukemia is a malignant neoplasm of the hematopoietic stem cells and is characterized by diffuse replacement of bone marrow by proliferating leukemic cells. Suppression of bone marrow by leukemic cells results in anemia. Leukemia can be developed by exposure to ionizing radiation, cytotoxic drugs, by exposure to benzene in industry, retroviruses and due to some genetic or immunological reasons. In case of the patients included in study, the underlying cause of leukemia was the use of cytotoxic drugs [20]. Different therapies like chemotherapy, biological therapy, targeted therapy, radiation therapy and stem cell transplant are used to treat leukemia. In case of the patients of leukemia under study, biological therapy and targeted therapy were used to treat leukemia. In case of biological therapy, body's immune system is activated against the leukemic cells whereas in case of targeted therapy, specific drugs are used to stop the growth of cancer cells by acting at specific targeted sites that are involved in the growth of cancer cells.

In case of anemia due to increased destruction of RBCs, thalassemia and systemic lupus erythematosus (types of congenital hemolytic anemia) were least prevalent amongst the

patients under study. Thalassemia is a hemolytic disorder in which the synthesis of globin chains is partially or completely suppressed resulting in reduced hemoglobin content in the red cells, which then have a short life span. Thalassemia though seen throughout the world is predominantly common in the individuals of Mediterranean origin, and Asian population [21]. It is mostly treated by blood transfusion. The thalassemic patient, under study, was prescribed to undergo blood transfusion twice a month. Systemic lupus erythematosus is an autoimmune disorder of connective tissue with variable features like fever, weakness, fatigability, joint pains and skin lesions on the face, neck or arms. It results in chronic inflammation due to autoantibody production [22]. Depending on the severity of disease, it can be treated by antimalarial agents, corticosteroids and immunosuppressive agents. In case of the patients included in study, corticosteroids were prescribed by the doctor. Hemolytic disease of new born develops when a Rh(D) negative woman conceives with a Rh(D) positive fetus. When the fetal red blood cells carrying D antigen enter the maternal blood circulation, maternal blood detects the antigen as a foreign body and produces antibodies against it. Initially being IgM antibodies are later replaced by IgG antibodies. These IgG antibodies enter the fetal blood when the same mother conceives with a Rh(D) fetus for the second time. These antibodies attach to the D antigens on the surface of the fetal red blood cells and form antigen antibody complexes. After about 20 weeks, fetal red cells to which the antibodies are attached, start hemolyzing. The fetal hemolysis possesses two problems i.e. fetal anemia due to decreased RBCs number and fetal hyperbilirubinaemia due to accumulation of bilirubin, which is a waste of hemoglobin destruction. Mostly anti-D IgG antibodies are used for the prophylaxis against Rh(D) isoimmunisation. In case of the babies with hemolytic disease of newborn either exchange blood transfusion is carried out or phenobarbital is administered to the newborn at the rate of 10mg/kg/24 hours to mature the liver enzyme system [23]. Amongst the patients of the hemolytic disease of new born who were included in the study, two died immediately after birth while condition of the newborn who survived, was critical and was referred to another hospital for better treatment.

In case of anemia due to blood loss, menorrhagia was the leading cause of anemia in adolescent girls. Anemia due to antepartum hemorrhage was specifically found in women of child bearing age [13]. Blood loss from GI tract was commonly found in patients who were either taking NSAIDS as a part of their medication or who had hemorrhoids. Dilated internal and external venous plexuses in the anal canal are known as hemorrhoids. They result from inadequate intake of fiber in diet [24]. In case of hemorrhoids, blood in stools leads to long term iron deficiency anemia. For external hemorrhoids firstly fiber and liquids are added to the diet of patient. Patient is made aware of self-care techniques. Ointments and creams are prescribed to stop itching and stool softeners are suggested to the patients, by practitioners for relief from constipation [25]. For the treatment of internal hemorrhoids, blood supply to the hemorrhoids is cut off. As a result hemorrhoids fall off within seven days of treatment. Injections (sclerotherapy) are also available for the treatment of internal hemorrhoids. Surgery is done when none of the treatments explained above, is effective. In case of the patients of hemorrhoids who were included in the study, surgery was performed as the patients didn't respond well to other treatments. In case of the patients with anemia due to operative blood loss, anemia due to child birth was due to loss of a large volume of blood during a caesarean section whereas anemia due to blood loss in surgery was found in case of patients who had undergone a hepatic surgery. Blood transfusion, being the most preferred treatment for anemia due to operative blood loss, was carried out in case of the patients, who were included in the study [26].

Trauma often results in loss of a large volume of blood that may result in anemia. In order to replenish the lost blood, blood transfusion is carried out. In case of the patients having anemia due to traumatic blood loss, blood transfusion was carried out. NSAIDs mostly result in erosion of the stomach wall or small intestine that causes GI bleeding [25]. Chronic blood loss may result in iron deficiency anemia. In case of the patients with anemia due to NSAID induced GI bleeding, treatment is offered depending on the acuity and severity of patient's signs as already observed by Ulas et al. [27].

Oral or parenteral iron therapy is recommended by the practitioner, depending on the condition of the patient. In case of the patients of anemia due to GI bleeding, parenteral iron therapy was preferred as it was better tolerated in patients and iron bioavailability is more in this case as compared to that from oral iron therapy [27].

CONCLUSION

This cohort study conducted on anemic patients proved that anemia was more prevalent in females as compared to males due to excessive blood loss that ultimately resulted in iron deficiency anemia. Children and adults were more prone to anemia as compared to the elderly patients. Children received an iron-poor diet in the growing age that led to iron deficiency anemia in them as well as they were brought up in poor hygienic conditions that became the cause of hookworm infestation in them. Development of anemia in adults was also due to poor dietary intake and due to excessive blood loss. In order to decrease the level of percentage of anemia in all age groups, healthy diet must be suggested by the practitioner. Patients must be advised to add food rich in iron (spinach, mustard leaves, turnip green, meat, fish and poultry), folic acid (liver, kidneys, fruits and vegetables) and vitamin B12 (meat, fish, eggs and milk) in their diet. Adolescent females should take iron supplements in order to replenish the monthly blood loss whereas pregnant women should undergo prophylactic iron therapy in order to avoid the development of anemia. Poor hygienic conditions add to the prevalence of anemia in all age groups so patients must be educated regarding hygiene and its effectiveness in the daily life.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

ACKNOWLEDGEMENTS

REFERENCES

1. Arthur S.Schneider and Philip A.Szanto. Anemia. BRS Pathology,4[th]Edition.11: 152, 2008.
2. Tolentino K. and Friedman J. F. An update on anemia in less developed countries. Am J Trop Med Hyg.;77(1):44-51, 2007.
3. Beutler E., Lichtman M. A., Coller B. S. Williamshematology. 6th ed. New York: McGraw-Hill; 2000.

4. Hoffman R., Benz E. J.Jr, Shattil S. J. Hematology: basic principles and practice. New York: Churchill Livingstone; 1998.
5. Asha Shah. Anemia. Indian Journal of Medical Sciences. 58 (1): 24-25, 2004.
6. Oliveira M. A., Osório M. M., Raposo M. C. Socioeconomic and dietary risk factors for anemia in children aged 6 to 59 months. J Pediatr (Rio J). 83(1): 39-46, 2007.
7. Lee G. R., Foerster J., Lukens J. Wintrobe's clinical hematology. 10th ed. Baltimore, Md: Lippincott, Williams & Wilkins; 1999.
8. Christian Nordqvist. What is anemia? What causes anemia? Medical News Today. 2009.
9. Anthony S. Fauci, Eugene Braunwald, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, Joseph Loscalzo. Harrison's Principles of Internal Medicine. 17th ed. United States: McGraw-Hill Professional, 2008.
10. Wang Z, Ma A, Xu D, Zou J. Comparison of haemoglobin level and anemia prevalence between female and male post-adolescent high school graduates. Wei Sheng Yan Jiu; 32 (2): 144-6, 2003.
11. Eugene Stransky and Florencio N. Quintos. On hookworm anemia. American society of hemotology. 2: 63-71, 1947.
12. Terri D. Johnson-Wimbley. Diagnosis and management of iron deficiency anemia in the 21st century. TherapAdvGastroenterol.; 4 (3): 173-184, 2011.
13. Ezechi Oliver and KalejaiyeOlufunto. Management of anemia in pregnancy. Anemia, 14: 233-46, 2012.
14. Alemayehu Abate, WubetBirhan and AbebeAlemu. Association of anemia and renal function test among diabetes mellitus patients attending FenoteSelam Hospital, West Gojam, Northwest Ethiopia: a cross sectional study. BMC Hematology, 13: 6, 2013.
15. McHutchison J. G., Manns M. P., Brown R. S. Jr., Reddy K. R., Shiffman M. L., Wong J. B. Strategies for managing anemia in hepatitis C patients undergoing antiviral therapy. Am J Gastroenterol.102(4):880-9, 2007.
16. Michael S. Gordon. Managing Anemia in the Cancer Patient: Old Problems, Future Solutions. The Oncologist. 7(4): 331-41, 2002.
17. M. R. Jeffrey. Anemia of Rheumatoid Arthritis. Ann Rheum Dis.; 11(2): 162–167, 1952.
18. Edith Lahner, Bruno Annibale. Pernicious anemia: New insights from a gastroenterologicalpoint of view. World J Gastroenterol.;15(41): 5121-5128, 2009.
19. ArshadChohan. Anemia in Pregnancy. Fundamentals of obstetrics,1st edition, 7: 89-95, 2005.
20. Mohammad Inam Danish. Blood. Textbook of pathology, 2nd Ed.,10: 118-120, 2006.
21. Sylvia T. Singer, Vivian Wu, Robert Mignacca, Frans A. Kuypers, Phyllis Morel and Elliott P. Vichinsky. Alloimmunization and erythrocyte autoimmunization in transfusion-dependent thalassemia patients of predominantly Asian descent. American society of hematology. 96: 3369-3373, 2000.
22. S.Giannouli, M.Voulgarelis, P. D.Ziakas and A. G.Tzioufas. Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. Ann Rheum Dis.; 65(2): 144–148, 2006.
23. ArshadChohan.Fetomaternal blood group incompatibility. Fundamentals of obstetrics,1st edition, 13: 159, 2005.
24. Arthur S.Schneider and Philip A.Szanto. Gastrointestinal tract. BRS Pathology, 4th Edition. 15: 227, 2008.
25. Paul Rutter.Gastroenterology. Community Pharmacy symptoms, diagnosis and treatment, 2nd ed., 6:127-129, 2008.

26. Stefan W. Leichtle, Nicolas J. Mouawad and Joseph J. Bander. Anemia and Transfusions in Surgical Patients: Current Concepts and Future Directions. J Blood DisordTransfus.,4172/2155-9864, 2011.

27. Ulas D. Bayraktar, SoleyBayraktar. Treatment of iron deficiency anemia associated with gastrointestinal tract diseases. World Journal of Gastroenterology; 16(22): 2720-2725, 2010.