European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 08, 2023

Original Research Article

EFFECT OF REPEATED BLOOD TRANSFUSIONS IN PATIENTS WITH CHRONIC BLOOD RELATED DISORDERS (INCLUDING THALASSEMIA AND SICKLE CELL DISEASE)

Aanavi Malik[1]*, Dr. Sofia Noor[2], Dr. Rudraksh Kesharwani[3]

[1]*Final Year MBBS student, Late Shri Lakhiram Agrawal Memorial Government Medical College, Raigarh
[2]Professor and Head of Department, Community Medicine, Late Shri Lakhiram Agrawal Memorial Government Medical College, Raigarh
[3]MBBS, Late Shri Lakhiram Agrawal Memorial Government Medical College, Raigarh)

***Corresponding Author: -** Aanavi Malik
*Final Year MBBS student, Late Shri Lakhiram Agrawal Memorial Government Medical College, Raigarh

Abstract:
Chronic blood transfusion therapy plays a crucial role in the management of various haematological disorders, such as thalassemia, sickle cell disease, and aplastic anaemia. However, repeated blood transfusions can lead to iron overload and subsequent complications, including hemochromatosis. This research aimed to test a screening protocol to identify chronic blood transfusion-related complications and prevent end-stage morbidities, specifically focusing on iron overload and its associated effects. The study will be conducted in Chhattisgarh, considering its high prevalence of blood disorders and the need for optimised transfusion practices.

1. Introduction:
1.1 Background:
Chhattisgarh has a significant burden of blood disorders, necessitating frequent blood transfusions. Chronic blood transfusion therapy, although life-saving, can lead to iron overload, resulting in complications like hemochromatosis. Early detection and management are crucial to preventing end-stage morbidities associated with chronic transfusion therapy.

1.2 Current Situation
Genetic blood disorders, such as thalassemia and sickle cell disease, pose a significant health burden in the state of Chhattisgarh. These conditions, although not affecting patients in utero, lead to lifelong disabilities and impose a substantial economic burden on individuals and their families. The prevalence of sickle cell trait and thalassemia trait is approximately 10% in the state's population, with the city having the highest carrier rate of 11.69% among districts with medical colleges.In order to treat their symptoms, patients with these genetic blood disorders frequently need blood transfusions. These transfusions could, however, result in complications. There are about 0.8 mg of iron in every millilitre of packed red blood cells. Due to their low ability to excrete iron (roughly 2 mg/day), patients who receive multiple transfusions can easily accumulate iron and develop hemochromatosis. The main organs affected by iron overload are the pancreas, liver, and heart. Organs, exposure duration, and the quantity of transfusions are some of the variables that affect how severe iron toxicity is.
Acquired hemochromatosis typically manifests first in the liver, then the pancreas, and finally the heart. Despite the fact that the idea of chronic iron overload brought on by blood transfusions is well understood, there are no established standards for screening patients at risk at this time.The Government of India initiative does not cover chelation therapy, despite it being essential for treating iron overload. Patients are required to cover their own expenses for any prescribed medications. Due

ISSN 2515-8260 Volume 10, Issue 08, 2023

to the lack of definitive guidelines and the cost constraints associated with iron profile screening, most patients in our institute, as well as in other similar institutions, receive regular transfusions without undergoing comprehensive screening. As a result, iron overload and its associated complications often go undetected until patients become symptomatic, leading to delayed intervention.

2. Review of Literature

2.1 Iron Overload and its Treatment Modalities:

According to Alan Cohen in his paper on Management of Iron Overload in the Pediatric Patient (1), if left untreated, excess iron can harm the body and eventually lead to death from heart disease. Desferrioxamine is an iron-chelating drug that removes iron from tissues, prevents iron-induced organ failure, and prolongs life. Proper administration of deferoxamine requires attention to dose, route and timing of administration, and compliance. Other ways to prevent or reduce iron buildup include changing the timing of blood transfusions or blood products.

2.2 Development of iron overload in the body

As mentioned in the paper by A. Remacha et al. (2), the body has a simple and effective way of controlling the intestinal absorption of iron, as well as the transport, eventual storage, and release of this iron through the blood, but there is no effective way to control the excretion of iron from the body. Iron overload is an inevitable and serious consequence of long-term transfusion and is directly related to the number of blood transfusions. One unit of red blood cell volume contains about 200–250 mg of iron. After about 8–10 sessions in a row, iron accumulates in the tissues and can cause poisoning. As iron overload worsens, the saturation capacity of transferrin is exceeded, and a fraction of iron not bound to transferrin is detected in the plasma. This ingredient is very toxic because it promotes free radical production and promotes iron uptake in tissues. Hydroxyl radicals induce cell death and fibrosis by inducing lipid peroxidation.

2.3 Requirement for guidelines and interventions

As written in the article by Shander, A. (3) patients on long-term therapy should be checked and monitored for excess iron, but this is not always done in hospitals. Once iron overload is identified, it must be treated to reduce the risk of morbidity and death, particularly from iron toxicity affecting the liver and heart. When the risk of iron overload from long-term therapy is known, more methods such as iron chelation should be used to reduce total body iron and the risk of long-term risk.

2.4 Iron overload trends in Thalassemia and Sickle cell disease

According to Radha Raghupathy's article in the Advances of haematology (4), in diseases such as sickle cell disease that often require blood transfusion, exogenous iron accumulates, circulates as non-transferrin bound iron (NTBI), enters the tissues, produces reactive oxygen species (ROS) and damages the body. However, compared to thalassemia patients, despite similar blood levels, SCD patients may be resistant to cardiovascular disease and endocrine gland toxicity. Ineffective erythropoiesis in thalassemia leads to iron overload, both directly and through regulation of other downstream pathways.

3. Aims and objectives

3.1 Aim:

Testing a screening protocol for transfusion-dependent patients to identify iron overload and plan timely intervention to prevent any morbidities

3.2 Primary objectives

1. Assess the prevalence of iron overload and hemochromatosis among transfusion-dependent patients.

ISSN 2515-8260 Volume 10, Issue 08, 2023

2. Investigate the clinical effects of iron overload and hemochromatosis.
3. Develop strategies to prevent and manage iron overload and subsequent complications.
4. To develop an effective diagnostic and screening protocol for the ill effects of chronic blood transfusion that can be applied to any low-resource setting.

3.3 Secondary objectives

1. To know the biochemical alterations and physiological dysfunctions associated with chronic blood transfusions.
2. To find the treatment burden, economic load, and prevalence of thalassemia and sickle cell disease in our area.
3. To establish a correlation between iron profile, amount of blood transfusion, and status of liver, pancreas, and heart.

4. Material and Methods

4.1 Design of study:

Hospital-based cross-sectional study

4.2 Place of study:

- The study was conducted under the Department of Medicine.
- The subjects who fulfilled the inclusion criteria were selected from various wards and ICUs

4.3 Duration of study:

- 6 months
- Institutional Ethics Committee clearance was obtained before starting the study

4.4 Study Subjects:

- Patients suffering from chronic blood transfusion-dependent Red Cell pathology
- Patients were subjected to various biochemical, pathological, and radiological analyses based on our designed study protocol.

4.5 Inclusion Criteria:

- Patients who are admitted to the hospital (wards and ICU) with diseases requiring chronic transfusion support (Thalassaemia and hemoglobinopathies, Sickle Cell anaemia; Hereditary spherocytosis and other membrane disorders, Pyruvate-kinase deficiency and other enzyme disorders, any other Haemolytic Anaemia)
- Patients who have received >10 units of packed red blood cells.
- Patients with no pre-diagnosed underlying etiologies that can alter our lab results. (for e.g.- If a Sickle Cell patient is admitted due to hepatitis then he will not be eligible for screening related to hepatic complications.)

4.6 Exclusion Criteria:

- Patients not giving consent.
- The patient who does not fulfil inclusion criteria.
- Patients with other underlying diseases
- Patients who are also suffering from infection, inflammation, hepatitis, hemolysis, or vitamin C deficiency (or any potential aetiology which can alter ferritin level) will be first subjected to C-reactive protein measurement and then, if found normal, may participate in the study.

ISSN 2515-8260 Volume 10, Issue 08, 2023

4.7 Study Instruments:

- A pretested questionnaire was used to collect socio-demographic details and other relevant data from the patient.
- The collected samples were sent for biochemical and haematological profiling.
- The patient was sent for an MRI liver, Chest X-ray, and ECG.

4.8 Sample Collection and Laboratory Testing:

The following tests were conducted

- Serum iron
- Total Iron Binding Capacity (TIBC)
- Unsaturated Iron Binding Capacity (UBIC)
- Transferrin saturation
- Serum ferritin
- Haematology
- Hb
- RBC indices
- RBC count - Hematocrit
- MCV - MCH
- MCHC
- RDW
- Total WBC count
- Differential WBC count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelet count

5. Observations and Results

5.1 Observations from the questionnaire (attached at the end of the document) and comprehensive history taking of chronic transfusion dependent patients

5.1.1 Transfusion History:

○ Most patients were admitted around once every 2-5 months for a transfusion, due to symptoms such as fainting, weakness, and joint pain.
○ The duration of hospital admission was usually 2-3 days, depending on how long it took to arrange blood for the patient.
○ Most patients received between 1-2 units of blood per visit, depending upon their build and severity of symptoms
○ This data on the frequency and duration of their visits, as well as the amount of blood they received, helped us assess the extent of their exposure to transfusion-related complications and iron overload.

5.1.2 Symptoms and Complications:

○ Asking about symptoms and other history of the patient gave us crucial information about the underlying disease of the patient.
○ They presented with symptoms, including but not limited to ■ fatigue.
■ shortness of breath.
■ muscle weakness.

ISSN 2515-8260 Volume 10, Issue 08, 2023

■ tachycardia
■ joint pain
○ We then proceeded to ask about any symptoms or complications related to sickle cell disease, such as pain crises, acute chest syndrome, stroke, or organ damage. These were used to indicate disease severity and the need for transfusions.

5.1.3 Transfusion Reactions:
We then inquired if the patient has experienced any adverse reactions to previous blood transfusions, such as
1. febrile reactions,
2. allergic reactions, or 3. transfusion-related infections.

5.1.4 Iron Overload Symptoms:
Symptoms associated with iron overload were asked about as well as looked for clinically (such as fatigue, joint pain, abdominal pain, and changes in skin pigmentation)

5.1.5 Family History:
We explored the family history of sickle cell disease or other blood disorders to assess the genetic risk and potential need for screening in family members.

5.1.6 Genetic Counselling:
Discuss whether the patient has received genetic counselling or testing for sickle cell disease or other genetic variants associated with the condition. This information can help guide treatment decisions and inform family planning.

5.1.7 Quality of Life:
Assess the patient's overall quality of life, including their ability to perform daily activities, attend school or work, and engage in social interactions. This provides insights into the impact of the disease and transfusion therapy on their well-being.
We observed that most of the patients requiring repeated blood transfusions had a significant impact of their morbidity on their day to day lives, including severe bouts of pain, unable to do regular heavy work. Most patients were aware of their blood disorder and the practicalities of it, but were unaware of how the repeated transfusions they received could affect them beyond the alleviation of their symptoms. Such a lack of awareness was also seen in the patients' attendants.

5.2 Frequency and severity of iron overload associated morbidities observed
For our research we took a pool of 100 patients. As depicted in figure 1, 29 of those patients were suffering from thalassemia , 51 were suffering from sickle cell disease and 20 had suffered through road traffic accidents.

ISSN 2515-8260 Volume 10, Issue 08, 2023

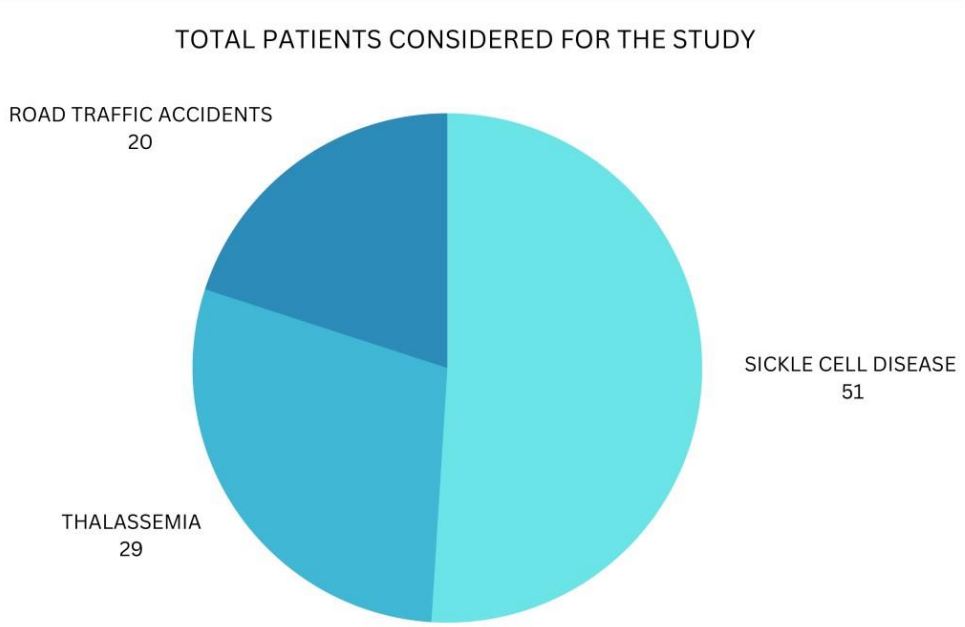


FIGURE 1.

Out of the patient pool, 25 patients showed signs and symptoms of iron overload. 14 of those patients were thalassemic, 10 were suffering from sickle cell disease and 1 was a road traffic accident survivor. These statistics have been represented in figure 2.

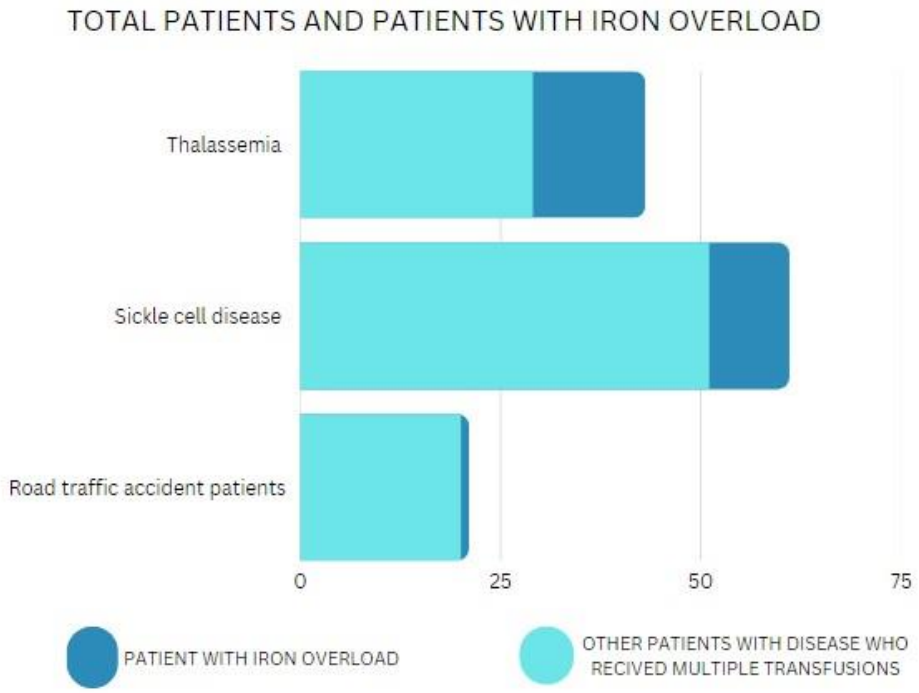


FIGURE 2

Overall we found that patients suffering from thalassemia were at maximum risk for developing iron overload. Patients with sickle cell anaemia developed iron overload symptoms to a lesser extent while development of iron overload in road traffic accident patients was a rarity.

ISSN 2515-8260 Volume 10, Issue 08, 2023

5.3 Screening protocol developed

A basic screening protocol has been developed by us on the basis of the protocol that we had proposed in the project proposal as shown in figure 4. This newly developed protocol has been given in figure 3.

This screening protocol is of special importance to thalassemia and sickle cell anaemia patients as well as patients with other haematological disorders that require them to receive repeated transfusion. Any patient who shows signs and symptoms of iron overload as mentioned above, should immediately be referred to the medicine department and started on chelation therapy.

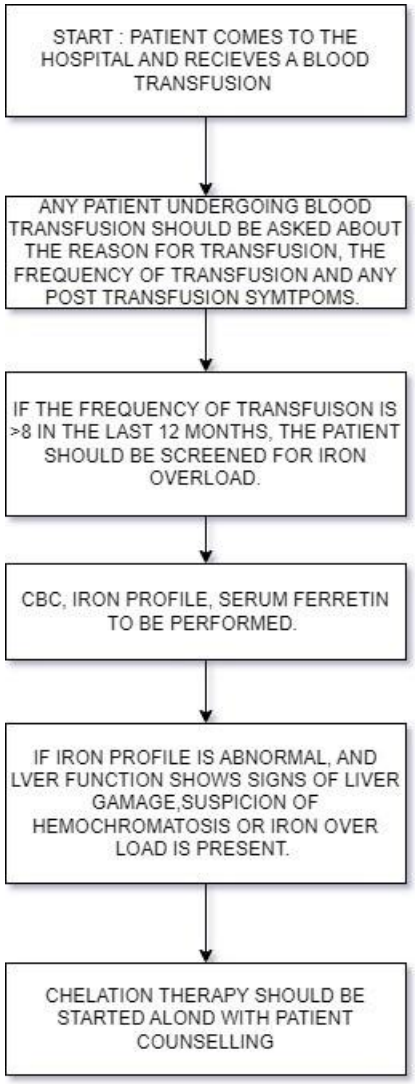
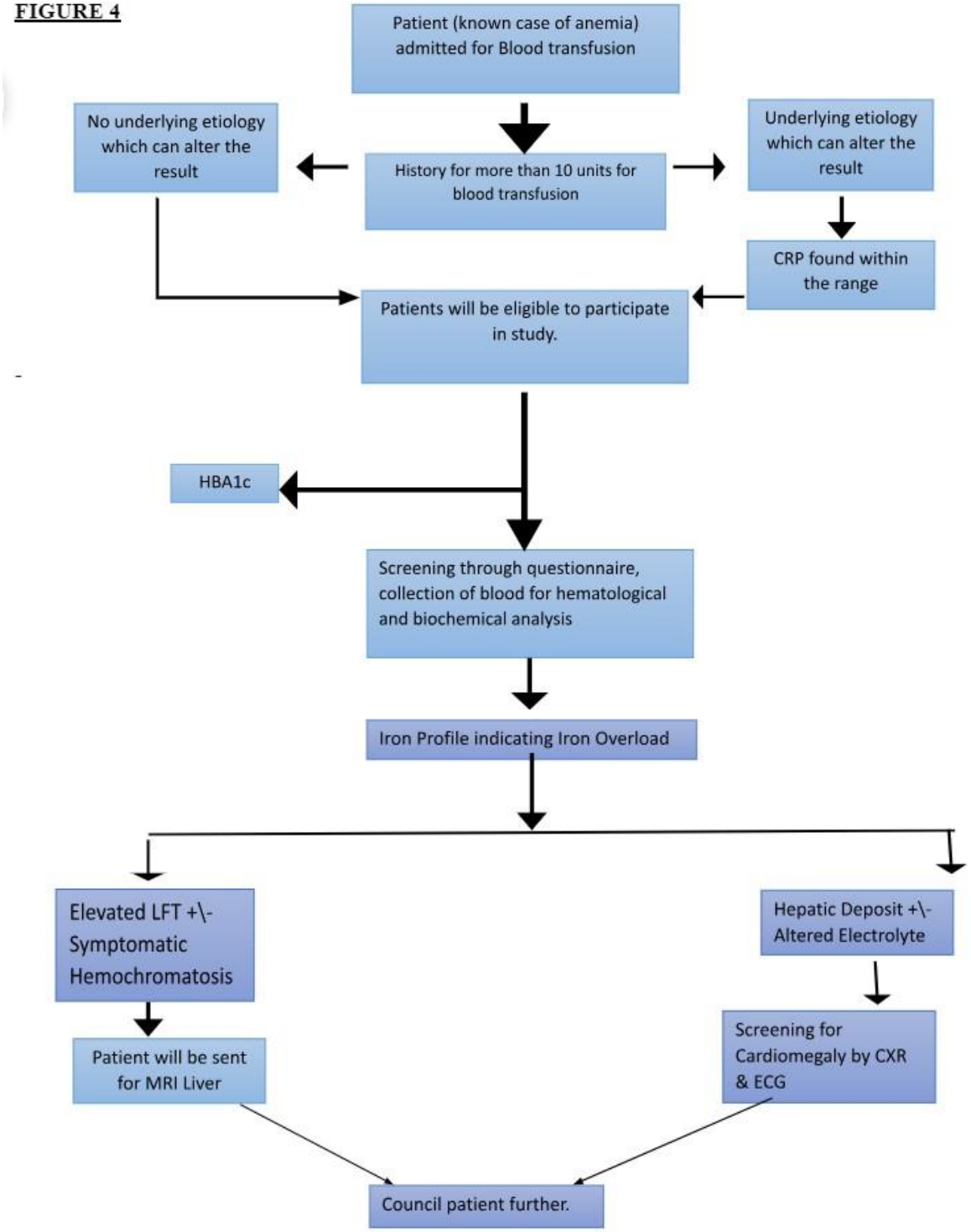


Figure 3.

ISSN 2515-8260 Volume 10, Issue 08, 2023

FIGURE 4



5.4 Relevant clinical cases

To illustrate the significance of the study, anonymous clinical cases of transfusion-dependent patients with iron overload and hemochromatosis are presented, highlighting the associated complications and the need for effective screening protocols.

Clinical Case 1: A 30-year-old patient with sickle cell disease who has been receiving chronic blood transfusions, once in 2 months for the past 10 years presents with fatigue, abdominal pain, and joint pain. Laboratory investigations reveal elevated serum ferritin levels and transferrin saturation. Further

ISSN 2515-8260 Volume 10, Issue 08, 2023

evaluation with imaging studies shows evidence of iron deposition in the liver. The patient is diagnosed with iron overload-associated liver disease, requiring chelation therapy to reduce iron levels and prevent further liver damage.

Clinical Case 2: A 25-year-old patient with sickle cell disease receiving chronic blood transfusions since childhood complains of shortness of breath and palpitations. Cardiac evaluation revealed cardiomegaly and reduced cardiac function. Iron overload-related cardiac dysfunction is suspected. Further assessment with echocardiography confirmed iron deposition in the heart. Chelation therapy was initiated to reduce cardiac iron levels and manage cardiac complications.

Clinical Case 3: A 35-year-old patient with sickle cell disease and a history of chronic blood transfusions presents with uncontrolled blood sugar levels and a recent diagnosis of diabetes mellitus. Further evaluation shows elevated HbA1c levels, indicating poor glucose control. Iron overload-associated diabetes mellitus is suspected, and the patient is counselled on lifestyle modifications, close glucose monitoring, and the importance of chelation therapy to manage iron overload and improve glycemic control.

5.5 Effectiveness of intervention methods

The effectiveness of intervention methods for chronic blood transfusion-related complications depends on the specific complications being addressed. Here are some commonly utilised intervention methods and their effectiveness in managing these complications:

1. **Chelation Therapy:**

Chelation therapy using iron-chelating agents, such as deferoxamine, deferasirox, and deferiprone, is effective in reducing iron overload in patients receiving chronic blood transfusions. It helps remove excess iron from the body and prevent or mitigate iron-related complications, such as liver disease and cardiomyopathy. Regular monitoring of iron levels and adjusting the chelation therapy regimen based on individual patient needs is crucial for optimal effectiveness.

2. **Disease-Modifying Treatments:**

Disease-modifying treatments, such as hydroxyurea for sickle cell disease or bone marrow transplantation for thalassemia, can effectively reduce the need for chronic blood transfusions. These treatments aim to modify the underlying disease process, minimise complications, and improve overall outcomes. Their effectiveness varies depending on the specific disease and individual patient factors.

3. **Supportive Care:**

Supportive care measures play a crucial role in managing chronic blood transfusion-related complications. This includes measures such as pain management, infection prevention, nutritional support, and regular monitoring of organ function. These interventions help improve the overall well-being of patients, reduce complications, and enhance their quality of life.

4. **Regular Monitoring and Follow-up:**

Regular monitoring of iron levels, organ function, and disease progression is essential for effective intervention. It allows healthcare providers to track the effectiveness of treatments, identify any changes or complications early on, and modify the management plan accordingly. Close follow-up and adherence to monitoring schedules are crucial for maximising the effectiveness of interventions.

5. **Patient Education and Counselling:**

Patient education and counselling are vital components of intervention methods. Providing patients and their families with information about the disease, its complications, and the importance of adherence to treatment plans can empower them to actively participate in their care. Education on

ISSN 2515-8260 Volume 10, Issue 08, 2023

lifestyle modifications, self-management techniques, and the importance of regular follow-up can significantly enhance the effectiveness of interventions.

It is important to note that the effectiveness of intervention methods can vary depending on individual patient factors, disease severity, and other variables. A multidisciplinary approach involving healthcare providers from various specialties is often necessary to tailor interventions to the specific needs of each patient and ensure optimal effectiveness.

5.6 Postulated benefits of the screening protocol

1. **Early intervention:** Patients receiving repeated blood transfusions can be screened and intervened before any significant comorbidities Screening protocols allow for preventive measures by identifying patients at risk for complications. For example, early initiation of chelation therapy for iron overload can help prevent or reduce iron-related problems such as liver disease and coronary artery disease
2. **Ease of administration of chelating agents:** An established system will facilitate the administration of chelating agents and other therapeutic modalities, ease of administration, and ease of monitoring of results.
3. **Early detection:** Screening protocols enable early detection of potential complications associated with chronic hemodialysis, such as iron overload and organ damage. Early detection of these complications can lead to timely intervention and management strategies to prevent end-stage disease progression
4. **Individualized patient care:** Assessment systems facilitate individual patient care by tailoring interventions based on the specific risk factor and its needs. It enables healthcare professionals to develop personalised treatment plans and monitoring strategies to optimise patient outcomes.
5. **Quality of life:** Identifying and managing chronic transfusion-related complications in a timely manner can significantly improve patients' quality of life by preventing or reducing end-stage diseases and leading to better overall health, reduced symptoms, and improved physical and functional well-being
6. **Cost-effectiveness:** a proper screening program can provide cost-effective healthcare delivery to patients with iron overload.

6. Discussion

The percentage of reperfused patients who develop iron overload can vary depending on many factors, including the underlying condition requiring transfusion, the frequency and duration of transfusion, and the characteristics of the individual patient

In our study, we found the following prevalence of iron overload associated with several conditions:

1. Thalassemia:

In patients with thalassemia major or other severe forms requiring regular blood transfusions, the prevalence of iron overload was 60% to 70% or even more so we knew that patients with thalassemia had a higher chance of iron overload.

2. Sickle cell disease:

Although iron overload is less common in sickle cell disease compared to thalassemia, iron can still accumulate from repeated transfusions The prevalence of iron overload in sickle cell disease is 10% to 30% in regularly transfused patients.

3. Major blood donation:

Trauma patients with high transfusion requirements, typically defined as blood volume exceeding their own blood volume over a 24-hour period, may be at increased risk for iron overload as a result of the high iron dose.

4. Longer hospital stays and more surgeries:

Trauma patients who have longer hospital stays, require more surgical procedures, and may receive multiple blood transfusions over a longer period of time. Under such conditions, there is the possibility of iron accumulation and subsequent iron overload.

It should be noted that these percentages are estimates and may vary depending on the treatment regimens used for the specific populations studied Routine monitoring of iron parameters, such as serum ferritin and transferrin.

Efficacy of chelation therapy, patient compliance, and availability of monitoring and monitoring resources in the healthcare system can all influence true prevalence of iron overload so diagnosing and treating iron overload in rehabilitation patients still depends on individual patient assessment and routine testing.

7. Conclusion

The screening protocol we have created was modified based on patient characteristics, institutional policies, and the resources that were available in collaboration with healthcare professionals. It performs well in settings with constrained resources and those where blood disorders are common. Every tertiary healthcare facility has a sickle cell unit where the use of these screening guidelines will aid in the early diagnosis and treatment of morbidity related to blood transfusions.

Before beginning the various treatment modalities for transfusion-related symptoms, the flowchart in figure 3. should be taken into consideration as a baseline.

8. Summary

This research report focuses on creating a screening process to detect and prevent complications associated with blood transfusions, particularly iron overload. These complications are quite common, among individuals with blood disorders like thalassemia and sickle cell disease.

The study was conducted in the state of Chhattisgarh due to its prevalence of blood disorders, which necessitates the implementation of transfusion procedures and practices. Excessive iron accumulation in the body can occur as a result of blood transfusions leading to organ damage such as liver and pancreas issues. Detecting and managing iron overload at a stage is crucial for avoiding health problems associated with long term transfusion therapy.

To assess iron overload and its related complications the researchers developed a screening protocol that incorporates pathological and radiological analyses. The study also provides examples of patients affected by iron overload while highlighting the importance of intervention techniques like chelation therapy treatments for system related conditions and supportive care.

The report emphasises the significance of detection and timely intervention as factors in improving patient outcomes and reducing healthcare expenses. However it acknowledges limitations in the study such, as a sample size and insufficient longitudinal data.

Healthcare professionals can greatly improve the quality of life for these patients. Prevent the advancement of health issues associated with excessive iron levels by implementing this screening procedure.

9. References

1. Alan Cohen, Management of Iron Overload in the Pediatric Patient, Hematology/Oncology Clinics of North America, Volume 1, Issue 3, 1987, Pages 521-544, ISSN 0889-8588, https://doi.org/10.1016/S0889-8588(18)30667-1. (https://www.sciencedirect.com/science/article/pii/S0889858818306671)
2. Remacha A, Sanz C, Contreras E, De Heredia CD, Grifols JR, Lozano M, Nuñez GM, Salinas R, Corral M, Villegas A; Spanish Society of Blood Transfusion; Spanish Society of Haematology and Haemotherapy. Guidelines on haemovigilance of post-transfusional iron overload. Blood Transfus.

2013 Jan;11(1):128-39. doi: 10.2450/2012.0114-11. Epub 2012 Jul 4. PMID: 22790272; PMCID: PMC3557483.

3. Shander, A., Cappellini, M.D. and Goodnough, L.T. (2009), Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox Sanguinis, 97: 185-197. https://doi.org/10.1111/j.1423-0410.2009.01207.x
4. Radha Raghupathy, Deepa Manwani, Jane A. Little, "Iron Overload in Sickle Cell Disease", Advances in Hematology, vol. 2010, Article ID 272940, 9 pages, 2010. https://doi.org/10.1155/2010/272940