Review Article

Updates on Management of transfusion induced Iron Over-load: A Systematic Review

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ABSTRACT

Multiple blood transfusions lead to an excess iron buildup in the body's organs, which damages the organs. This systematic review investigated the recently published approaches to manage transfusion-induced iron overload. PubMed, SCOPUS, Web of Science, Science Direct, and Cochrane Library were systematically searched to include the relevant literature. Rayyan QRCI was used throughout this systematic approach. Our results included eleven studies with a total of 1635 patients diagnosed with transfusional iron overload. Iron excess is a major challenge in patients with chronic anemia who require frequent transfusions. Evidence from numerous clinical trials has shown that giving chelation therapy to individuals with transfusion-induced iron overload clearly reduced their iron burden and improved organ function. We found that Amlodipine, lupatercept, and chelating agents are safe and effective options for transfusion dependant thalassemia (TDT) patients. Additionally, Amlodipine or lupatercept combined with chelating agents are more efficient in lowering serum ferritin and o regularly drank green tea experienced significant reductions in iron accumulation. Deferiprone (DFP) has provided sickle cell disease (SCD) patients with a new therapeutic choice. The effects of this oral iron chelator were equivalent to those of deferoxamine (DFX) given subcutaneously in terms of reducing transfusional iron excess. In line with what had previously been seen in thalassemia syndrome patients, DFP showed a tolerable safety profile.

Keyword: Iron overload; Blood transfusion; Chelation; Management; Systematic review.

Introduction

Concerns about transfusion iron excess are crucial when treating patients with severe anemic disorders like thalassemia. Extra iron from multiple blood transfusions deposits in different body organs and harms them. Early iron chelation therapy can stop serious, potentially fatal consequences [1]. Blood transfusion frequency is directly correlated with extra iron from transfusion. A blood transfusion unit normally contains 200-250 mg of iron. Patients who get 10 to 20 units of blood are frequently at danger of iron excess. Patients suffering from thalassemia, myelodysplastic syndrome, sickle cell disease, aplastic anemia, and other blood disorders who become transfusion-dependent eventually develop iron overload [2]. Transfusion iron overload incidence varies widely depending on the level of early detection and preventative treatments. According to cardiac MRI data (myocardial T2* of 20 milliseconds), 925 individuals with transfusion-dependent thalassemia, myocardial iron excess was found in 36.7% of the patients. When compared to patients from the Middle East, patients from the West and the Far East had a higher iron load in their hearts [3].

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Blood transfusions are required on a regular basis for over 15,000 Americans with sickle cell disease and 4500 persons with myelodysplastic syndromes and other refractory anemias. On a worldwide basis, the figure is close to 100,000 [4]. The body cannot effectively get rid itself of extra iron through physiological means. The reticuloendothelial macrophage phagocytose senescent red blood cells (RBCs) when they occur. The RBC's heme component disintegrates into iron and protoporphyrin inside the macrophage. Free iron is released into plasma. The primary iron transport protein, serum transferrin, then binds to two molecules of iron (Fe3+) from plasma. Due to transferrin saturation, non-transferring -bound iron (NTBI) and labile plasma iron (LPI) enter organs via L-type calcium channels (LCC), ZIP14, and divalent metal transporter (DMT1) [5]. Depending on the duration of the transfusion dependency as well as the severity of the underlying disease, transfusion iron overload is managed. Patient adherence is a key factor in therapy outcomes. To increase patient compliance, the treatment plan should be modified. It is best to start iron chelation treatment as a preventative measure before clinically significant iron overload occurs. The majority of patients are already anemic; therefore, phlebotomy is typically avoided. An iron-chelating agent is typically started after 15 to 20 units of blood transfusions. In USA, DFX and DFS are frequently employed. The preferred treatment for transfusion iron excess is DFX. It is given as a subcutaneous or continuous intravenous infusion. It chelates tissue and circulating iron in the body and excretes it in the urine and bile. DFS, on the other hand, is an oral iron chelator. DFX is absorbed by the hepatocytes and other tissues after ingestion. DFS removes tissue iron primarily in bile after chelating it [6]. The majority of patients typically handle iron-chelating medications effectively. The majority of side effects are dosage-dependent and are simply avoidable by changing the dose. To monitor chelation-related toxicity, routine testing should be run. If any issues develop, stop taking the current medicine and reassess. This systematic review looked at the newly published approaches to manage transfusion-induced iron overload.

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses): this is a guidline to help reviewers for reporting systematic review [7].

Study Design and Duration: This systematic review was carried out in August 2023.

Strategy for searching: A complete search was conducted in five significant databases, such as Google Scholar, Web of Science, PubMed, Science straight, and EBSCO, to find the pertinent studies. Our search was restricted to English, and we took into consideration the specific requirements of each database. In order to discover relevant research, the next keywords were changed into terms for PubMed Mesh: "Sickle cell, Malaria, Plasmodium falciparum, Hemoglobin." To match the key phrases, the Boolean operators "OR" and "AND" were applied. Publicly accessible articles, human trials, and publications, the search results met everything in English.

Choice criteria

For this review, we took consideration of the following factors:

- Study designs that investigated the recently published approaches to manage transfusion-induced iron overload.
- Patients with anemic disorders (not oncologic conditions).
- Studies conducted between 2019-2023.
- No age limits were restricted.
- English language.
- Free accessible articles.

Data extraction: In the search strategy's output, duplicates were found using Rayyan (QCRI) [8]. The researchers filtered the combined search results using a set of inclusion/exclusion criteria to assess the relevancy of the titles and abstracts. Each paper that meets the requirements for inclusion has been examined carefully by the reviewers. The writers presented additional methods for resolving disputes after serious thought. The authors were able to get information on the studies' titles, authors, research year, country, participants, gender, diagnostic tool, main findings, and conclusion.

Method for synthesizing data: To give a qualitative summary of the research's results and main elements, utilizing information from pertinent studies, summary tables were created. Once the data from the systematic review was retrieved, the most effective way to use the data from the included study articles was determined.

Results

The systematic search yielded 705 study papers, of which 77 duplicates were removed. On 628 studies, title and abstract screening were performed, and 520 studies were eliminated. Only 8 items were not recovered out of 108 that were searched for retrieval. Finally, 100 papers were examined for full-text evaluation; 55 were removed due to incorrect research outcomes, as well as 31 for the incorrect population category. This systematic review comprised fourteen study papers. In, a synopsis of the research selection procedure is provided (Figure 1).

Characteristics of the included studies: The sociodemographic characteristics of the collected study articles are shown in (Table 1). Our findings included thirteen trials including a total of 1635 participants diagnosed with transfusion-induced iron

overload. Four studies were multi-centered [12, 15, 19, 20], two people in India [11, 13], two people in Iraq [14, 22], one people in Iran [9], one people in Brazil [10], one people in Pakistan [16], one in people Italy [17], one people in Brazil [18], and one people in Egypt [21]. Eight studies were randomized control trials (RCTs) [9, 11, 12, 14-16, 19, 20]. (Table 2) presents the clinical characteristics. Ten studies discussed the management of iron overload on transfusion-dependent β-thalassemia (TDT). Amlodipine (calcium channel blocker) is safe and more efficient than chelation therapy alone in lowering cardiac iron overload and serum ferritin [9, 11]. Chelation therapy significantly decreased cardiac siderosis. Ferritin levels and myocardial iron overload improve sooner than liver iron in the subset of chelation therapy patients with moderate/severe liver iron concentration [10, 13, 16, 17-18]. The use of lupatercept(erythroid maturation agent) caused clinically substantial decreases in serum ferritin levels, liver iron concentration, and myocardial iron levels, indicating a lower risk of iron overload problems [12, 15]. Interestingly, regular green tea consumption significantly improved iron deposition in thalassemia intermedia patients receiving DFS iron chelation therapy [14]. SCD patients now have a new therapy option thanks to DFP. This oral iron chelator significantly decreased transfusional iron excess, and its results were comparable to those of DFX administered subcutaneously. DFP demonstrated a tolerable safety profile that was in line with what had previously been observed in thalassemia syndrome patients [19-22].

Discussion

Early diagnosis and observance of preventative measures have a substantial impact on the prognosis of patients with iron overload. For instance, it takes about 1.5 months to lower the iron content in the liver by half, whereas it takes approximately Thirteen months to do so in the heart [23]. Since the development of preventive iron chelating treatment (ICT), Patients with transfusion iron excess have improved in terms of quality of life and survival [24]. However, mortality from transfusion-induced iron excess is three times higher than in the general population [25]. This study found that Amlodipine is safe and more efficient than chelation therapy alone in lowering cardiac iron overload and serum ferritin in TDT patients [10, 12]. Iron content in human tissues may not be sufficiently removed by iron chelator monotherapy or combination therapy [26]. A systematic evaluation of two randomized controlled trials (n = 74) found that amlodipine medication significantly increased myocardial relaxation compared to the control group. Due to the poor quality of the available data, the findings remained unresolved [27]. The findings of additional clinical studies looking at the effectiveness and potency of amlodipine on iron deposition in cardiac cells may help to develop a suitable procedure and set of guidelines for treating thalassemia cases with mild to severe cardiac siderosis brought on by iron overload. Chelation therapy significantly decreased cardiac siderosis. Ferritin levels and myocardial iron overload improve sooner than liver iron in the subset of chelation therapy patients with moderate/severe liver iron concentration [10, 13, 16, 17-18]. In particular, patients with -thalassemia major have been proven to benefit from iron chelation therapy when they have transfusion-dependent anaemia. Numerous observational studies and one small randomised trial have shown that iron chelators can be used to maintain low serum ferritin levels, which can reduce end-organ damage and increase survival in patients with transfusion-dependent anemia [28, 29]. Regular green tea consumption significantly improved Iron accumulation in people with thalassemia intermedia receiving DFS iron chelation therapy [14]. The primary component of green tea is polyphenols, which account for 24–36% of the dry weight. These polyphenol compounds, which block iron (heme and non-heme) absorption by gastrointestinal cells, are primarily composed of catechins. Individuals regularly taking green tea could result in an extraordinarily low iron balance [30]. The antioxidant abilities of green tea may also have an impact on SF [31]. However, a recent experiment in which curcumin was added to green tea for those with thalassemia found a modest rise in serum ferritin after two months; the authors are unsure of this cause [32].

SCD patients now have a new therapy option thanks to DFP. This oral iron chelator significantly decreased transfusional iron excess, and its results were comparable to those of DFX administered subcutaneously. DFP demonstrated a tolerable safety profile that was in line with what had previously been observed in thalassemia syndrome patients [19-22]. DFP immediately enters the circulation after being swiftly absorbed, primarily from the stomach. However, food-drug interactions or other gastrointestinal variables may cause the drug's absorption into the blood after oral administration to be delayed. Wide differences in deferiprone metabolism and clearance have been seen in patients, primarily as a result iron overload and the supply of chelatable iron [33]. Because of its low therapeutic index and safety issues, such as the potential of agranulocytosis, [34, 35], this medication is not permitted in the USA and Canada. It is, however, allowed for use as a second-line therapy for iron excess in various Asian and European countries.

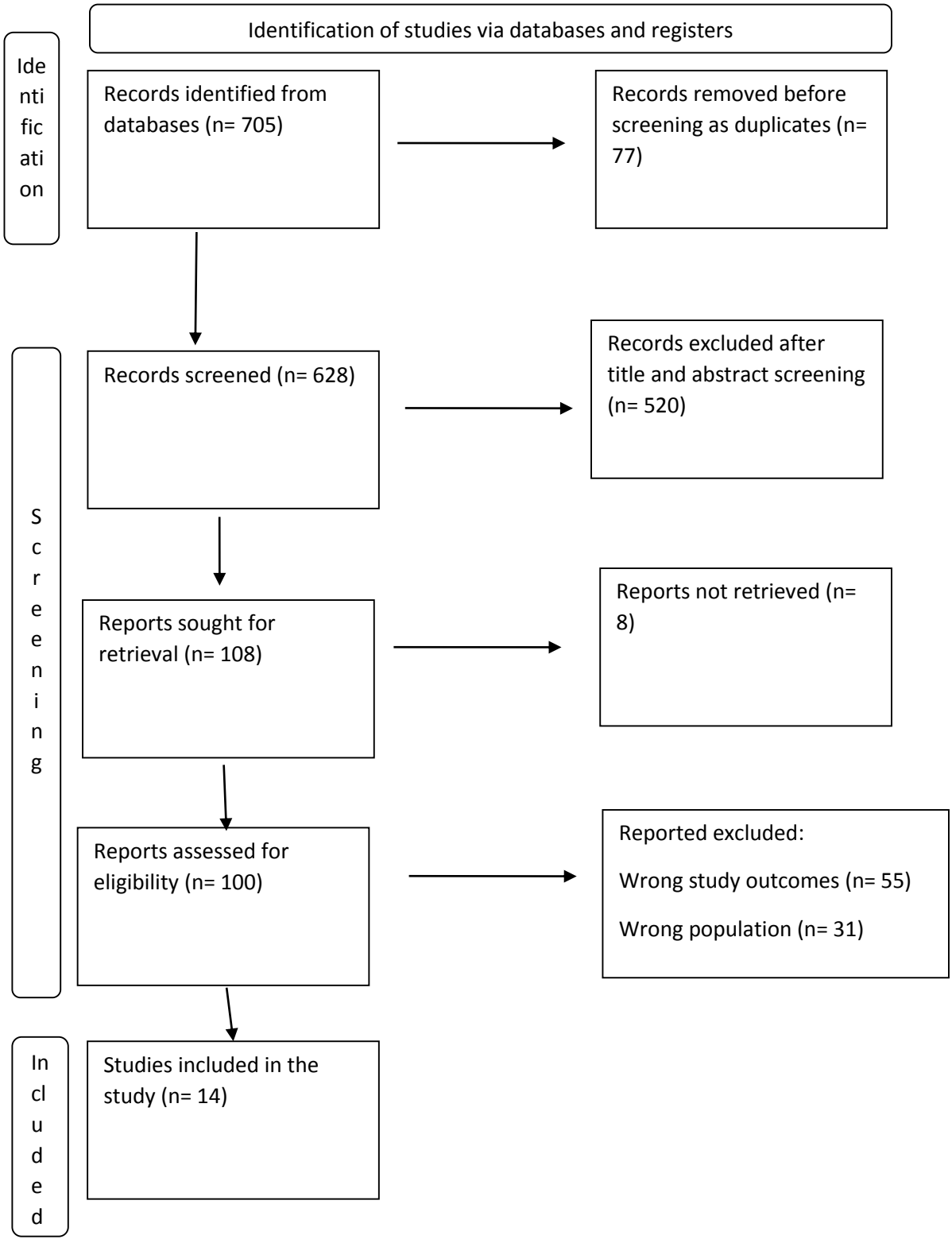

Figure (1): Prisma chart for studies selection.

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age (years)	Males (%)
Karami et al. 2021 [9]	RCT	Iran	17	28.4 ± 5.9	11 (64.7)
Chapchap et al. 2023 [10]	Cross-sectional	Brazil	136	7-55 (range)	47 (34)
Gupta et al. 2022 [11]	RCT	India	64	10.66 ± 3.54	50 (78.1)
Porter et al. 2019 [12]	RCT	Multi-centered	308	NM	NM
Karami et al. 2021 [13]	Observational prospective	India	21	7.8 ± 2.5	14 (67)
Al-Momen et al. 2020 [14]	RCT	Iraq	57	13.62±4.27	29 (50.8)
Hermine et al. 2020 [15]	RCT	Multi-centered	224	NM	NM
Hussain et al. 2020 [16]	RCT	Pakistan	100	9-34 (range)	56 (56)
Origa et al. 2022 [17]	Retrospective cohort	Italy	16	38 ± 6	5 (31.3)
Takpradit et al. 2021 [18]	Prospective cohort	Thailand	9	13-20 (range)	7 (77.8)
Kwiatkowski et al. 2019 [19]	RCT	Multi-centered	228	16.9 ± 9.6	121 (53.1)
Kwiatkowski et al. 2022 [20]	RCT	Multi-centered	228	16.9 ± 9.6	121 (53.1)
Elalfy et al. 2023 [21]	Prospective cohort	Egypt	134	16.2 ± 8.6	81 (60.4)
Abdul-Hassan et al. 2019 [22]	Clinical observational	Iraq	93	81.54±15.27	52 (55.91)

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Disorder	Medication	Conclusion
Karami et al. 2021 [9]	TDT	Amlodipine (5 mg, daily) + chelation	Prescribing amlodipine in addition to standard chelator therapy is beneficial because it may enhance myocardial MRI T2* and serum ferritin levels in comparison to a placebo.
Chapchap et al. 2023 [10]	β-thalassemia	Iron chelation	Hepatic (99%) and cardiac (36%) siderosis are common in young adults with thalassemia major who receive standard transfusion protocols. In thalassaemic patients, chelation therapy significantly decreased cardiac siderosis. Ferritin levels and myocardial iron overload seem to improve sooner than liver iron in the subset of chelation therapy patients with moderate/severe liver iron concentration (LIC).
Gupta et al. 2022 [11]	TDT	Amlodipine (5 mg, daily) + chelation	In children and young adults with TDT, amlodipine is safe and considered to be more efficient than chelation therapy alone in lowering cardiac iron overload.
Porter et al. 2019 [12]	β-thalassemia	Luspatercept	The use of lupatercept caused clinically substantial decreases in serum ferritin levels. No matter the baseline serum ferritin level, LIC, or myocardial iron loading, the treatment led to clinically significant decreases in the burden of RBC transfusions, suggesting that baseline iron overload did not appear to impair responsiveness to luspatercept.
Karami et al. 2021 [13]	TDT	combined oral chelation with DFP and DFX	In children with severe iron overload, combined oral chelation with DFP and DFS significantly lowers the serum ferritin level. The medications were well tolerated and had no significant negative side effects.
Al-Momen et al. 2020 [14]	β-thalassemia	Green tee + chelation therapy	In thalassemia intermedia patients receiving DFS iron chelation therapy, regular green tea consumption significantly improved iron deposition.
Hermine et al. 2020 [15]	β-thalassemia	Luspatercept	During the first 48 weeks, a higher percentage of luspatercept-treated patients switched to lower blood ferritin, liver iron concentration, and myocardial iron levels, indicating a lower risk of iron overload problems.
Hussain et al. 2020 [16]	β-thalassemia	Quality-improved chelation therapy	The cardiac status of TDT patients' at participating centers' improved as a result of better chelation therapy provided by QI initiatives.

Origa et al. 2022 [17]	β-thalassemia	Combined iron chelation	In patients with iron overload who do not respond to monotherapies, both of the more recent combination iron chelation treatments can be taken into consideration. There don't seem to be any substantial safety or tolerability issues with either therapy. As long as therapy compliance is at least average, the effect of both therapies on hepatic iron seems to be more immediate and noticeable than the effect on cardiac iron.
Takpradit et al. 2021 [18]	β-thalassemia	DFX and DFO	For TDT patients who had not responded to conventional IC therapy, the combination of DFX and DFO proved to be successful and free from major toxicities. To clarify the effectiveness of the combination, additional research with a bigger cohort size and long-term follow-up is required.
Kwiatkowski et al. 2019 [19]	SCD	DFX, DFO, and DFP	Changes in hepatic iron content indicate that DFP is equally effective as DFO in treating iron excess in people with SCD or other uncommon anemias. The myocardial iron load and SF Endpoints supported non-inferiority. The use of DFP was not linked to any unforeseen major side effects, and its safety profile was satisfactory and comparable to that previously observed in thalassemia patients.
Kwiatkowski et al. 2022 [20]	SCD	DFP	Patients who suffer from SCD and other uncommon anemias with transfusional iron excess now have a new therapy option thanks to DFP. This oral iron chelator significantly decreased transfusional iron excess, and its results were comparable to those of DFX administered subcutaneously. DFP demonstrated a tolerable safety profile that was in line with what had previously been observed in thalassemia syndrome patients.
Elalfy et al. 2023 [21]	SCD	DFP	Individuals with SCD or other anemias who received long-term DFP medication noticed that their iron load continue to decline over time without experiencing any additional safety issues.
Abdul-Hassan et al. 2019 [22]	TDT and SCD	DFX	DFS has been proven to be a safe, tolerable, and effective medication for lowering iron overload, although it can be more effective if safety markers and serum ferritin are monitored to ensure proper drug dose.

Conclusion

In patients with chronic anemia who require frequent transfusions, iron excess is a major challenge. Evidence from numerous clinical trials has shown that giving chelation therapy to individuals with iron excess caused by transfusion clearly reduced their iron burden and improved organ function. Amlodipine, lupatercept, and chelating agents are safe and effective options for TDT. Additionally, Amlodipine or lupatercept combined with chelating agents are more efficient in lowering serum ferritin and liver and myocardial iron overload. Patients with thalassemia intermedia receiving DFS iron chelation therapy who regularly drank green tea experienced significant reductions in iron accumulation. DFP has provided SCD patients with a new therapeutic choice. The effects of this oral iron chelator were equivalent to those of DFX given subcutaneously in terms of reducing transfusional iron excess. In line with what had previously been seen in thalassemia syndrome patients, DFP showed a tolerable safety profile.

Conflict of Interest

None

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None

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