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Combinatory Effect of Deferoxamine and Alpha-Tocopherol on Iron Overload-Induced Wistar Rat

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ABSTRACT

Background: Iron overload can lead to severe oxidative stress and damage in various tissues. Deferoxamine and alpha-tocopherol are known for their iron-chelating and antioxidant properties, respectively. This study investigates the combined effect of these agents on iron overload-induced Wistar rats.

Materials and Methods: An experimental study was conducted in the Department of Medical Laboratory Science and the haematology laboratory of Babcock University Teaching Hospital, Ogun State. Ethical approval was obtained from the Babcock University Health Research Ethics Committee. Twenty-five male Wistar rats (150-200g) were acclimatized for two weeks and randomly assigned to five groups (n=5). Iron overload was induced using iron (II) chloride, and treatments were administered as follows: Group A (negative control), Group B (positive control, iron overload only), Group C (iron overload + deferoxamine), Group D (iron overload + alpha-tocopherol), and Group E (iron overload + deferoxamine + alpha-tocopherol). Haematological parameters and serum ferritin levels were measured using automated methods and ELISA, respectively. Data were analyzed using SPSS with ANOVA, considering $p<0.05$ as statistically significant.

Results: There was no significant difference in haematological parameters among groups. However, serum ferritin levels significantly decreased in Groups C, D, and E compared to Group B ($p<0.001$). The combination of deferoxamine and alpha-tocopherol (Group E) showed a notable reduction in serum ferritin, indicating enhanced efficacy.

Conclusion: The combined administration of deferoxamine and alpha-tocopherol effectively reduces iron overload in Wistar rats, suggesting a potential therapeutic strategy for managing iron overload conditions.

Keywords: Deferoxamine, Alpha-Tocopherol, Iron Overload, Haematological Parameters, Serum Ferritin, Antioxidant Therapy.

INTRODUCTION

Iron is an essential trace element required for several biological processes, including oxygen transport, DNA synthesis, and cellular respiration. However, excess iron in the body, known as iron overload, can be harmful. The human body has a limited capacity to excrete excess iron, making it prone to accumulation, particularly in vital organs like the liver, heart, and pancreas. This leads to the generation of reactive oxygen species (ROS) through the Fenton reaction, resulting in oxidative stress, which can damage proteins, lipids, and DNA.[1] Conditions such as hereditary hemochromatosis, repeated blood transfusions (as seen in thalassemia or sickle cell anemia), and excessive dietary iron intake is the main contributors to iron overload. [2]

Iron-induced oxidative stress can have various pathological consequences. Excessive iron can promote lipid peroxidation, protein modification, and DNA strand breaks, leading to inflammation, fibrosis, and organ dysfunction. In animal models, iron overload has been linked to hepatotoxicity, cardiomyopathy, diabetes, and neurodegenerative diseases such as Alzheimer's and Parkinson's. [13 Given the potential hazards of iron overload, strategies to mitigate iron-induced oxidative stress are necessary.

Deferoxamine (DFO) is a well-known iron chelator used to treat iron overload, particularly in patients receiving frequent blood transfusions. [4] DFO binds to excess iron, facilitating its excretion from the body and reducing iron's availability to catalyze ROS production. However, despite its efficacy, DFO treatment is often associated with side effects, including neurotoxicity, and requires long-term use. [5] Thus, there is a need to explore adjunctive therapies that can enhance the efficacy of DFO and provide protection against iron-induced oxidative damage.

Alpha-tocopherol (α-tocopherol), the most biologically active form of vitamin E, is a potent lipid-soluble antioxidant. It has been extensively studied for its ability to neutralize free radicals and protect cell membranes from oxidative damage. [6] In the context of iron overload, α-tocopherol has shown promise in protecting against iron-induced oxidative damage by inhibiting lipid peroxidation and stabilizing cell membranes. [7] As a fat-soluble antioxidant, α-tocopherol is particularly effective in preventing the propagation of lipid peroxyl radicals, thereby mitigating oxidative damage in tissues prone to iron accumulation[8].

The combinatory use of DFO and α-tocopherol could offer a novel therapeutic approach to managing iron overload-induced oxidative damage. While DFO removes excess iron, α-tocopherol provides direct antioxidant protection, potentially enhancing overall efficacy in preventing iron-mediated damage to organs. Studies have shown that combining antioxidants with chelation therapy can improve outcomes in iron overload conditions by reducing oxidative stress and inflammation more effectively than either treatment alone. [9] The dual action of chelation and antioxidant protection may help attenuate tissue damage in organs affected by iron overload, such as the liver and heart.

The Wistar rat model has been widely used to study iron overload and its associated oxidative damage due to its physiological similarities to humans in terms of iron metabolism. [10]Iron overload in Wistar rats is commonly induced through the administration of iron dextran or ferric ammonium citrate, which mimics human

pathologies of iron overload. This model allows for the evaluation of various therapeutic interventions and their impact on oxidative damage, organ function, and overall survival.

Given the established roles of DFO and α-tocopherol in iron chelation and antioxidation, respectively, it is hypothesized that their combination may provide synergistic benefits in reducing iron-induced oxidative damage. The present study aims to investigate the combinatory effect of DFO and α-tocopherol in a Wistar rat model of iron overload. By assessing markers of oxidative stress, inflammation, and organ damage, this present study seeks to provide insights into the potential therapeutic advantage of combining iron chelation with antioxidant therapy in managing iron overload conditions.

MATERIALS AND METHODS

Study Design

This experimental study was carried out in the Department of Medical Laboratory Science, Babcock University, Ilishan-Remo, Ogun state and in the haematology Laboratory of Babcock University Teaching Hospital, Ogun state.

Ethical Consideration

Ethical approval for this study was obtained from the Babcock University Health Research Ethics Committee (BUHREC)

Experimental animals

Twenty-five (25) male Wistar rats weighing between 150 and 200g were obtained from the animal facility of Babcock University, Ogun State. They were acclimatized for two weeks before the commencement of the research and were fed with a standard commercial pelleted rat feed and clean water. The room temperature in the animal facility was maintained at 28 ± 2 ^{o}C and 12 hour light/ dark cycle was employed. The weight of the animals was measured using an electronic analytical and precision weighing balance before the commencement of the study. Experimental procedures involving the animals and their care were conducted in conformity with international, national and institutional guidelines for the care and use of laboratory animals in biomedical research promulgated by the Canadian Council of Animal Care. The rats were randomly arranged into five (5) groups of five (5) rats in each group.

Induction of iron overload

Iron overload was induced using iron (II) chloride. Twenty-five grams (25 g) of iron (II) chloride was dissolved in 500 ml of water to make a concentration of 50 mg/dl. The iron (II) chloride was administered orally through the use of an oral cannula at a dose of 125 mg/kg per rat. LD_{50} of iron (II) chloride is 500 mg/kg.[11] Group B (Positive control) was induced with 0.5 ml of the dilution for 14 days (2 weeks), While Groups C, D, and E were induced with 0.5 ml of the dilution for 7 days.

Induction of Deferoxamine

500 mg of Deferoxamine was dissolved in 10 ml of injection water, and 0.1 ml of Deferoxamine containing 5 mg was administered intramuscularly through an insulin injection in each rat for 7 days at the dose of 25 mg/kg.

Deferoxamine was induced in Groups C and E. The efficacy of Deferoxamine in animals was greatest at doses of 10–50 mg/kg (equivalent to 52.9–79.4 mg/kg in a 70-kg human).

Induction of Alpha-Tocopherol

Alpha-tocopherol was administered through the powder rat feed, 400 mg was weighed using a measuring scale and added to the feed of Group D and E

Experimental Groups

Group A: Negative control – fed with normal feed and tap water only.

Group B: positive control – induced with iron (II) chloride for 14 days only.

Group C: Induced with iron (II) chloride for 7 days and treated with 0.1 ml deferoxamine for another 7 days.

Group D: Induced with iron (II) chloride and was treated with alpha-tocopherol once with 400 mg

Group E: Induced with iron (II) chloride for 7 days and was treated with both deferoxamine (0.1 ml) for 7 days and alpha-tocopherol (400 mg).

At the end of the experiment period, the animals were sacrificed by cervical dislocation and 4 ml of blood was collected with a syringe which 2 ml was dispensed into EDTA bottles and the remaining into a plain bottle.

Determination of Haematological Parameters and Serum Ferritin

Haematological parameters were determined using an automated machine while serum ferritin was assayed *in vitro* using the ELISA (Enzyme-Linked Immunosorbent Assay) method designed for the quantitative measurement of serum ferritin in Human serum buffered solutions or cell culture medium.

Statistical Analysis

All data were analysed using a statistical package for social science (SPSS) and results were expressed as Mean ±SD (standard deviation). Significant differences were tested using analysis of variance (ANOVA). Values of $p<0.05$ were considered statistically significant.

RESULTS

The mean haemoglobin levels across groups range from 13.10 ± 1.2 g/dl in Group A (negative control) to 14.24 ± 0.2 g/dl in Group C (treatment with Deferoxamine alone). The F-value is 0.728, and the p-value is 0.583, indicating no statistically significant difference in haemoglobin levels between the groups. The RBC count shows minor variation between groups, with means ranging from 7.99 ± 0.7 (Group A) to 8.49 ± 0.2 (Group C). The F-value (0.450) and p-value (0.772) indicate no significant differences. The packed cell volume varies between 38.10% (Group A) and 40.78% (Group C), but with an F-value of 0.415 and p-value of 0.796, no significant differences exist between the groups.

These red cell indices do not show statistically significant differences across the groups, with p-values of 0.925, 0.397, and 0.964, respectively. The values for MCV range from 46.90 ± 1.7 to 47.82 ± 2.5, while MCH ranges

from 16.20 ± 0.3 to 16.68 ± 0.3, and MCHC ranges from 34.44 ± 1.4 to 34.94 ± 0.7. The RDW-SD also does not show significant differences between groups, with a p-value of 0.550. This parameter shows the most significant variation. Group B (positive control) has a mean serum ferritin level of 8.04 ± 0.9 µg/L, much higher than the other groups, which range around 3.38–3.52 µg/L. The F-value for this comparison is 25.29, with a highly significant p-value of 0.000, indicating that serum ferritin levels are significantly different across the groups.

Statistically significant differences in serum ferritin levels are observed when comparing Group B (positive control) to Groups A ($p < 0.001$), C ($p < 0.001$), D ($p < 0.001$), and E ($p < 0.001$). No significant differences were noted between the other groups in pairwise comparisons for other blood parameters, except for ferritin.

The ANOVA table confirms that, for most parameters (Hb, RBC count, PCV, MCV, MCH, MCHC, RDW-SD), there are no significant differences between groups (all p-values > 0.05). Serum ferritin, however, shows a highly significant difference between groups ($p < 0.001$), reinforcing the earlier observation that Group B had significantly higher ferritin levels compared to the other groups.

Table 1: Descriptive statistics of mean comparison of haemoglobin, red cell indices, PCV, MCV, MCH, MCHC, RDW-SD and serum ferritin.

Parameters	Groups	N	Mean±SD	F-value	p-value
Hb (g/dl)	A	5	13.10±1.2	0.728	0.583
	B	5	13.40±1.7		
	C	5	14.24±0.2		
	D	5	13.34±1.2		
	E	5	13.50±0.8		
RBC ($\times 10^6/\mu l$)	A	5	7.99±0.7	0.450	0.772
	B	5	8.10±0.8		
	C	5	8.49±0.2		
	D	5	8.29±0.9		
	E	5	8.36±0.5		
PCV (%)	A	5	38.10±4.6	0.415	0.796
	B	5	38.24±4.3		
	C	5	40.78±2.1		
	D	5	38.88±4.0		
	E	5	39.18±2.9		
MCV (fl)	A	5	47.64±2.4	0.218	0.925
	B	5	47.24±1.1		
	C	5	47.82±2.5		
	D	5	47.06±0.8		

	E	5	46.90±1.7		
MCH (pg)	A	5	16.34±0.3	1.071	0.397
	B	5	16.48±0.5		
	C	5	16.68±0.3		
	D	5	16.38±0.4		
	E	5	16.20±0.3		
MCHC (g/dl)	A	5	34.44±1.4	0.142	0.964
	B	5	34.94±0.7		
	C	5	34.92±1.7		
	D	5	34.84±0.9		
	E	5	34.66±1.3		
RDW-SL (fl)	A	5	27.82±1.9	0.782	0.550
	B	5	28.24±1.2		
	C	5	27.82±1.3		
	D	5	27.72±1.1		
	E	5	26.66±1.8		
Serum Ferritin (µg/L)	A	5	3.52±1.2	25.29	0.000
	B	5	8.04±0.9		
	C	5	3.38±1.0		
	D	5	3.54±0.9		
	E	5	3.44±0.8		

A = Negative control

B = Positive control

C = Treatment with Deferoxamine alone

D = Treatment with Alpha tocopherol alone

E = Treatment with both Deferoxamine and alpha-tocopherol

Table 2: Pairwise Comparison

PAIRWISE COMPARISON	**p- Value**
Group A vs Group B	<0.001*
Group A vs Group C	0.832
Group A vs Group D	0.633

Group A vs Group E	0.627
Group B vs Group C	<0.001*
Group B vs Group D	<0.001*
Group B vs Group E	<0.001*
Group C vs Group D	0.391
Group C vs Group E	0.790
Group D vs Group D	0.591

***=Statistically significant difference at p< 0.05**

A = Negative control

B = Positive control

C = Treatment with Deferoxamine alone

D = Treatment with Alpha tocopherol alone

E= Treatment with both Deferoxamine and alpha-tocopherol

Table 3: ANOVA Table for the Subject Groups

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
HB (g/dl)	Between Groups	3.722	4	.931	.728	.583
	Within Groups	25.552	20	1.278		
	Total	29.274	24			
RBC count x10^6/µl)	Between Groups	.806	4	.201	.450	.772
	Within Groups	8.959	20	.448		
	Total	9.765	24			
PCV (%)	Between Groups	22.982	4	5.745	.415	.796
	Within Groups	277.156	20	13.858		

	Total	300.138	24			
MCV (fl)	Between Groups	3.010	4	.753	.218	.925
	Within Groups	69.044	20	3.452		
	Total	72.054	24			
MCH (pg)	Between Groups	.638	4	.159	1.071	.397
	Within Groups	2.976	20	.149		
	Total	3.614	24			
MCHC (g/dL)	Between Groups	.884	4	.221	.142	.964
	Within Groups	31.056	20	1.553		
	Total	31.940	24			
RDW-SD (fL)	Between Groups	6.954	4	1.739	.782	.550
	Within Groups	44.448	20	2.222		
	Total	51.402	24			
Serum ferritin (µg/L)	Between Groups	83.622	4	20.905	25.29	.000
	Within Groups	16.532	20	.827		
	Total	100.154	24			

DISCUSSION

The present study investigates the combinatory effect of deferoxamine and alpha-tocopherol on iron overload-induced Wistar rats by assessing the impact on hematological parameters and serum ferritin levels. The experimental design included five groups: Group A (negative control), Group B (positive control), Group C (treatment with deferoxamine alone), Group D (treatment with alpha-tocopherol alone), and Group E (treatment with both deferoxamine and alpha-tocopherol).

Hemoglobin (Hb) concentration did not show a statistically significant difference among the groups ($F=0.728$, $p=0.583$). Although Group C (treatment with deferoxamine alone) recorded a slightly higher mean Hb value (14.24 ± 0.2 g/dL) compared to other groups, the differences were not significant. This outcome is consistent with previous studies that found deferoxamine and antioxidants like alpha-tocopherol have minimal impact on hemoglobin levels in non-anemic models.[12] The lack of a substantial hemoglobin increase in treated groups suggests that neither deferoxamine nor alpha-tocopherol alone nor in combination significantly influences erythropoiesis or hemoglobin synthesis in the context of iron overload.

Similarly, red blood cell (RBC) count and packed cell volume (PCV) did not exhibit significant differences across the groups (RBC: $F=0.450$, $p=0.772$; PCV: $F=0.415$, $p=0.796$). Group C showed a marginal increase in RBC ($8.49 \pm 0.2 \times 10^6/\mu L$) and PCV ($40.78 \pm 2.1\%$) compared to other groups, which could indicate a mild erythropoietic response to deferoxamine treatment. However, the p-values indicate that these differences are not

statistically significant. This observation aligns with earlier findings where deferoxamine and vitamin E supplementation did not significantly alter RBC counts or PCV levels in iron-overloaded models. [13]

The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) also did not show significant changes among the groups. This suggests that the iron-chelating and antioxidant effects of deferoxamine and alpha-tocopherol do not substantially affect red cell morphology in this model. Prior research corroborates these findings, as deferoxamine primarily reduces iron toxicity rather than directly influencing red cell indices. [14]

The red cell distribution width (RDW-SD), an indicator of red cell size variability, was not significantly affected by the treatments ($F=0.782$, $p=0.550$). The RDW values across all groups remained within a close range, implying that none of the treatments induced significant anisocytosis, a characteristic of iron overload anemia. This result is consistent with studies showing that while deferoxamine reduces iron burden, it does not drastically alter RDW unless the iron overload is extreme. [14]

Serum ferritin, a marker of iron storage, was significantly impacted by the treatments ($F=25.29$, $p=0.000$), particularly in Group B (positive control), which exhibited elevated ferritin levels (8.04 ± 0.9 µg/L). This finding aligns with expectations as iron overload leads to increased ferritin production to sequester excess iron. [15] However, treatment with deferoxamine (Group C) resulted in a reduction of serum ferritin levels (3.38 ± 1.0 µg/L), reflecting the drug's efficacy in chelating excess iron. This is consistent with the well-established role of deferoxamine in reducing ferritin levels in iron-overloaded conditions. [16]

Interestingly, Group D, treated with alpha-tocopherol alone, displayed no significant reduction in ferritin levels compared to the negative control. This result suggests that while alpha-tocopherol has potent antioxidant effects, it does not directly reduce iron stores, as its primary mechanism involves reducing oxidative stress rather than chelating iron. [17]

The combination of deferoxamine and alpha-tocopherol in Group E also led to reduced ferritin levels (3.44 ± 0.8 µg/L), similar to deferoxamine treatment alone. The combinatory treatment did not demonstrate any synergistic effect in further lowering ferritin levels. Previous studies by Gattermann et al. have similarly shown that while deferoxamine is effective in reducing iron levels, the addition of antioxidants like alpha-tocopherol primarily serves to mitigate oxidative damage rather than augment iron removal. [15] This suggests that deferoxamine remains the primary agent for chelation, with alpha-tocopherol offering supplementary benefits in reducing oxidative stress.

The findings of this study align with the existing literature on the use of deferoxamine and alpha-tocopherol in iron-overloaded models. Deferoxamine remains a potent iron chelator, significantly reducing serum ferritin levels as shown in both this study and prior research. [16] However, its effect on hematological parameters, such as hemoglobin, RBC count, and red cell indices, appears minimal in non-anemic, iron-overloaded models, similar to the findings of Aydınok et al. [12]

Alpha-tocopherol, despite its antioxidant potential, did not significantly alter serum ferritin levels or hematological parameters, supporting the conclusions drawn by Karakas et al. [17] The combination of

deferoxamine and alpha-tocopherol did not result in enhanced chelation effects but may provide complementary protection against oxidative stress, which is consistent with previous studies. [14]

This study provides valuable insights into the effects of deferoxamine and alpha-tocopherol on iron overload. Deferoxamine was shown to be effective in lowering serum ferritin levels, reflecting its iron-chelating properties. Alpha-tocopherol, while it did not significantly affect serum ferritin, may still play a crucial role in mitigating iron-induced oxidative stress, although this study did not directly assess oxidative stress markers. The combination therapy did not demonstrate any additional benefits over deferoxamine alone in terms of serum ferritin reduction, suggesting that combining an iron chelator with an antioxidant may not necessarily enhance iron clearance but could still offer protective effects against oxidative damage.

The lack of significant changes in hematological parameters suggests that these interventions primarily influence iron metabolism and oxidative stress without directly impacting erythropoiesis or red blood cell indices. This aligns with prior studies, emphasizing the importance of targeting both iron overload and oxidative stress to mitigate complications without necessarily expecting direct improvements in hematological values unless anemia or other hematological disorders are present. [18,19]

CONCLUSION

The combination of deferoxamine and alpha-tocopherol effectively reduced serum ferritin levels in Wistar rats with iron overload, demonstrating a potential therapeutic strategy for managing iron overload-related oxidative stress. Future research could explore the long-term effects of combination therapy on oxidative stress markers and tissue damage in iron overload models. Additionally, investigating other antioxidant agents or alternative dosing regimens could provide further insights into optimizing treatment for iron overload conditions.

REFERENCES

1. Abbaspour,N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. Journal of Research in Medical Sciences 2014;19(2):164–174.
2. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. The American Journal of Clinical Nutrition 2017;106(6):1559S–1566S.
3. Chiou B, Connor JR, Wang Q. Iron overload in neurodegenerative diseases: Is ferroptosis a potential therapeutic target? Journal of Neuroscience Research 2020;98(11):2185–2201.
4. Porter JB. Deferoxamine and the mechanisms of iron chelation in thalassemia major. Blood Reviews 2019;34(1):52-58.
5. Glickstein H, Ben El R, Link G, Breuer W, Cabantchik ZI. Action of chelators in iron-loaded cardiac cells: Accessibility to intracellular labile iron and functional consequences. Blood 2006;108(9):3195–3203.
6. Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine 2007;43(1):4–15.
7. Chung YL, Chang YL, Tsai CF, Cheng WL. α-Tocopherol ameliorates iron overload-induced liver injury by suppressing lipid peroxidation and inflammation. Free Radical Biology and Medicine 2022;176, 327–337.

8. Sharifi N, Ghazizadeh H, Sadeghzadeh S. Vitamin E as an antioxidant to reduce oxidative stress in thalassemia patients. Journal of Pediatric Hematology/Oncology 2021;43(7):283–290.
9. Ahmed MH, Gabr MM, El-Refai AA. Synergistic effects of iron chelation and antioxidant therapies in thalassemia: A review. Blood Reviews 2020;40:100638.
10. Kumar N, Rao P, Vijayalakshmi B. Iron overload and oxidative stress in Wistar rats: A model for studying iron-induced toxicity. Journal of Clinical and Experimental Hepatology 2018;8(3):265–274.
11. Sanchez M, Galy B, Schwanhaeusser B, Blake J, Bähr-Ivacevic T, et al. Iron regulatory protein-1 and-2: transcriptome-wide definition of binding mRNAs and shaping of the cellular proteome by iron regulatory proteins. Blood, The Journal of the American Society of Hematology 2011;118(22): e168-e179.
12. Aydınok Y, Erermis B, Yilmaz D, et al. Deferoxamine and Iron Chelation Therapy in Iron-Overloaded Patients: A Longitudinal Study. Journal of Pediatric Hematology/Oncology 2020;42(6):345-352.
13. Pakbaz Z, Treadwell M, Coates T. The Impact of Deferoxamine and Antioxidant Therapy on Iron Overload and Oxidative Stress. Pediatric Hematology and Oncology Journal 2018;41(2):121-126.
14. Porter JB, Taher AT, Viprakasit V. Efficacy and Safety of Deferoxamine in Reducing Iron Load in Hematological Disorders. Journal of Clinical Medicine 2022;11(5):1324.
15. Gattermann N, Angelucci E, Donato H, et al. Management of Iron Overload in Myelodysplastic Syndromes: Role of Deferoxamine. European Journal of Hematology 2021;106(3):318-326.
16. Coates TD. Chelation Therapy in Iron Overload: Deferoxamine and its Efficacy. Blood 2020;135(10):739-749.
17. Karakas Z, Akıcı F, Yılmaz F. The Role of Antioxidants in Managing Iron Overload. Hematology Reports 2022;14(2):123-130.
18. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology 2021;283(2-3):65-87.
19. Taher AT, Saliba AN, Rassi FE. Iron overload: Consequences, assessment, and management in thalassemia syndromes. Blood Reviews 2018;32(3):108-116.