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Effects of Chronic Inhalation of Carbon Monoxide on Some Haematological Parameters and Carboxyhaemoglobin Levels in Wistar Rats

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Abstract
Chronic exposure to carbon monoxide (CO) has been linked to various health issues, including alterations in blood parameters. This study aimed to investigate the effects of chronic inhalation of CO on haematological parameters and carboxyhaemoglobin levels in Wistar rats. Twenty healthy Wistar rats were acclimatized for 7 days and divided into four groups: Group A (control, no CO exposure), Group B (1-week exposure), Group C (2 weeks exposure), and Group D (3 weeks exposure). The rats in the exposure groups were placed in poorly ventilated cages with kerosene lanterns emitting CO. Blood samples were collected at the end of the exposure period for haematological analysis and carboxyhaemoglobin (COHb) measurement. Haematological parameters were analyzed using an automated haematology analyzer, and COHb levels were determined using spectrophotometry. Statistical analyses were performed using SPSS, including one-way ANOVA and Pearson's correlation. Significant increases in haemoglobin (Hb), red blood cell (RBC) count, packed cell volume (PCV), and COHb levels were observed in the exposed groups compared to the control group ($p<0.001$). MCV showed a negative correlation with COHb ($p=0.049$), while Hb, RBC, PCV, and MCHC showed positive correlations ($p<0.001$ to $p=0.015$). No significant changes were observed in MCH ($p=0.813$). Chronic inhalation of CO significantly affects haematological parameters, with increased levels of Hb, RBC, PCV, and COHb. These changes highlight the potential health risks associated with prolonged exposure to CO, emphasizing the need for effective mitigation strategies in environments with CO exposure.

Keywords: Carbon monoxide, Carboxyhaemoglobin, Haematological parameters, Chronic exposure, Spectrophotometry.

Introduction

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas that results from the incomplete combustion of carbon-containing materials, including fossil fuels, wood, and tobacco (Dolan *et al*., 2019). It poses significant environmental and public health risks due to its prevalence in urban environments, especially in regions with high vehicular emissions and industrial activities (Arif & Khan, 2020). Chronic exposure to carbon monoxide, even at low levels, can have deleterious effects on health, particularly on the cardiovascular and haematological systems (Raub & Benignus, 2021).

CO exposure is especially concerning because it binds with haemoglobin (Hb) to form carboxyhaemoglobin (COHb), reducing the blood's oxygen-carrying capacity (Hampson, 2019). As CO has a greater affinity for haemoglobin than oxygen, prolonged exposure leads to an increase in COHb levels, which can result in tissue hypoxia (Guan *et al.,* 2022). This effect is most pronounced in organs with high oxygen demands, such as the brain and heart, but it also has significant impacts on blood parameters (Wang *et al.,* 2020).

Chronic inhalation of carbon monoxide can affect various haematological parameters, including red blood cell (RBC) count, haemoglobin concentration, haematocrit, and white blood cell (WBC) count (Hasanpour-

Dehkordi *et al.,* 2018). Studies have shown that prolonged CO exposure often leads to polycythemia, a compensatory mechanism in response to chronic hypoxia, where the body increases RBC production to maintain oxygen delivery to tissues (Thom *et al.,* 2021). However, this adaptive response may lead to blood viscosity and associated complications, such as thrombosis (de Araujo *et al.*, 2021).

Further, WBC counts may be altered, with evidence suggesting a rise in inflammatory markers due to CO-induced oxidative stress and tissue damage (Lee *et al*., 2019). CO exposure also interferes with platelet function, increasing the risk of coagulation disorders and cardiovascular complications (Zhong *et al*., 2022).

The formation of COHb is a central feature of CO poisoning, which can be acute or chronic, depending on the exposure levels (Gorman *et al*., 2022). COHb levels as low as 5% can lead to mild symptoms such as headache and dizziness, while levels above 15% are associated with more severe effects, including confusion, loss of consciousness, and even death (Hampson & Weaver, 2018). Chronic exposure, often seen in urban workers or residents of industrial areas, may result in persistently elevated COHb levels, leading to chronic hypoxemia and associated health complications (Zhu *et al*., 2020).

Experimental models using Wistar rats have been valuable in understanding the pathophysiological effects of CO exposure. Rodents share physiological similarities with humans, making them appropriate for studying the effects of environmental pollutants like CO (Ding *et al.,* 2018). In these models, researchers have observed alterations in COHb levels and haematological parameters similar to those found in humans, highlighting the translational relevance of such studies (Chung *et al*., 2021).

Given the increasing levels of environmental pollution, particularly in developing countries, understanding the chronic effects of CO exposure on haematological parameters and COHb levels is essential. In regions with poor air quality management, populations may be exposed to CO concentrations that have significant health impacts over time (Peters *et al*., 2019). This study will contribute to a growing body of literature aimed at characterizing the haematological effects of chronic CO exposure, providing insights that could inform public health interventions and policies aimed at reducing CO-related morbidity and mortality.

In particular, this research will examine the effects of chronic CO inhalation on some haematological parameters and carboxyhaemoglobin levels in Wistar rats. This will enhance our understanding of the biological impacts of chronic low-dose CO exposure, which is often overlooked but is significant in populations exposed to urban and occupational CO sources.

Materials and Methods

Experimental Design

Twenty (20) healthy Wistar rats were used for this study. They were acclimatized for 7 days and were divided into four groups of rats each. Animals in group A were not exposed to carbon monoxide and served as the normal control group. Those in groups B, C and D were exposed to carbon monoxide one hour per day for 7, 14 and 21 days respectively. Each test group exposed to carbon monoxide were placed in poorly ventilated wooden cages, in each cage, kerosene lanterns (source of carbon monoxide) were placed to disperse the gas. They were covered with glass lids to ensure that there was no escape of gas.

At the end of the experimental period, the rats were humanely sacrificed and dissected open and whole blood was collected from the heart through the left ventricle. The whole blood was dispensed into a labelled anticoagulant bottle containing K3 EDTA (Tri-potassium Ethylene diamine tetra acetic acid) that binds and chelates calcium to prevent blood coagulation. The anticoagulant bottles containing whole blood were rocked gently to mix evenly with the anticoagulant and prevent clotting, they were taken to the Haematology Laboratory Department of Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, Nigeria for analysis at the haematological parameters. The laboratory analysis for the carboxyhaemoglobin levels was carried out in the H**a**ematology/Blood Group serology unit of the Department of Medical Laboratory Science, Babcock University, Ilishan-Remo, Ogun State, Nigeria.

Figure 1: **Kerosene Lanterns used for the Experiment**

Laboratory Analysis

Hematological parameters were determined by automation using an automated haematology analyser. Carboxyhaemoglobin levels were determined using a spectrophotometric method as outlined by Boumba *et al*. (2005).

Statistical Analysis

The data collected was entered into a Microsoft Excel sheet. Statistical analysis was carried out using SPSS (Statistical Package for Social Sciences) version 20.0. One-way Analysis of variance (ANOVA) was used between all groups and the data derived was represented appropriately in tables, and figures. Pearson's correlation was used to establish the association between carboxyhaemoglobin and blood parameters.

Ethical Consideration

Ethical clearance was obtained from the Babcock University Health Research Ethics Committee (BUHREC) with reference number BUHREC 356/21 before the commencement of the study.

Results

Table 1 presents the effects of carbon monoxide (CO) exposure on various haematological parameters. There is a statistically significant increase in Hb levels with longer exposure to CO ($p < 0.001$). Group D (3 weeks exposure) has the highest mean Hb (15.80±0.6 g/dl), while Group A (control) has the lowest mean Hb (13.08±0.6 g/dl). RBC counts also significantly increase with prolonged CO exposure ($p < 0.001$). Group D has the highest mean RBC (9.29±0.5 $\times 10^6/\mu l$), compared to Group A with the lowest ($7.68 \pm 0.6 \times 10^6/\mu l$).

PCV levels rise significantly with CO exposure ($p < 0.001$), with Group D showing the highest mean PCV (45.00±1.4%) and Group A the lowest (38.84±1.5%). Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH) show no significant changes across groups ($p = 0.166$ and $p = 0.926$, respectively). There is a significant increase in MCHC with CO exposure ($p < 0.007$), with Group D showing the highest mean MCHC (35.54±0.8 g/dl). COHb levels significantly increase with longer CO exposure ($p < 0.001$), with Group D having the highest COHb (8.31±0.6%) and Group A the lowest (1.95±0.4%).

Figures 2 to 7 summarize the correlation between carboxyhaemoglobin and blood parameters. Significant positive correlations are found between COHb and Hb ($r = 0.823$, $p < 0.001$), RBC ($r = 0.822$, $p < 0.001$), PCV ($r = 0.810$, $p < 0.001$), and MCHC ($r = 0.535$, $p = 0.015$). This indicates that higher COHb levels are associated with increased values of these parameters. Conversely, COHb shows a significant negative correlation with MCV ($r = -0.446$, $p = 0.049$), suggesting that as COHb increases, MCV tends to decrease.

Table 1: Effect of Carbon Monoxide (CO) on Haematological Parameters

Parameters	Groups	N	Mean±SD	p-value
Hb (g/dl)	A	5	13.08±0.6	<0.001*
	B	5	13.94±0.7	
	C	5	15.50±0.5	
	D	5	15.80±0.6	
RBC ($\times 10^6$/µl)	A	5	7.68±0.6	<0.001*
	B	5	8.29±0.2	
	C	5	8.87±0.3	
	D	5	9.29±0.5	
PCV (%)	A	5	38.84±1.5	<0.001*
	B	5	41.82±2.1	
	C	5	46.44±1.5	
	D	5	45.00±1.4	
MCV (fL)	A	5	50.72±2.6	0.166
	B	5	50.41±1.4	
	C	5	49.16±3.3	
	D	5	47.28±2.3	
MCH (pg)	A	5	17.04±0.7	0.926
	B	5	16.88±0.4	
	C	5	16.98±0.8	
	D	5	16.78±0.7	
MCHC (g/dl)	A	5	33.76±0.6	<0.007*
	B	5	33.57±0.7	
	C	5	34.98±1.2	
	D	5	35.54±0.8	
COHb (%)	A	5	1.95±0.4	<0.001*
	B	5	6.12±0.8	
	C	5	7.54±0.7	
	D	5	8.31±0.6	

*= statistically significant difference at p< 0.05; A= Control; B, C and D = 1-, 2- & 3-weeks exposure

Table 2: Pairwise Comparison Among Groups of Each Parameter

Parameters	Pairwise comparison			p –value
Hb (g/dl)	Group A	vs	Group B	<0.024*
			Group C	<0.001*
			Group D	<0.001*
	Group B	vs	Group C	<0.005*
			Group D	<0.001*
	Group C	vs	Group D	1.000
RBC ($\times 10^6/\mu l$)	Group A	vs	Group B	0.180
			Group C	<0.002*
			Group D	<0.001*
	Group B	vs	Group C	0.211
			Group D	<0.007*
	Group C	vs	Group D	0.714
PCV (%)	Group A	vs	Group B	0.070
			Group C	<0.001*
			Group D	<0.001*
	Group B	vs	Group C	<0.003*
			Group D	<0.047*
	Group C	vs	Group D	1.000
MCHC (g/dl)	Group A	vs	Group B	1.000
			Group C	0.272
			Group D	<0.036*
	Group B	vs	Group C	0.139
			Group D	<0.018
	Group C	vs	Group D	1.000
COHb (%)	Group A	vs	Group B	<0.001*
			Group C	<0.001*
			Group D	<0.001*
	Group B	vs	Group C	<0.016*
			Group D	<0.00*
	Group C	vs	Group D	0.435

*= statistically significant difference at p< 0.05; A= Control; B, C and D = 1-, 2- & 3-weeks exposure

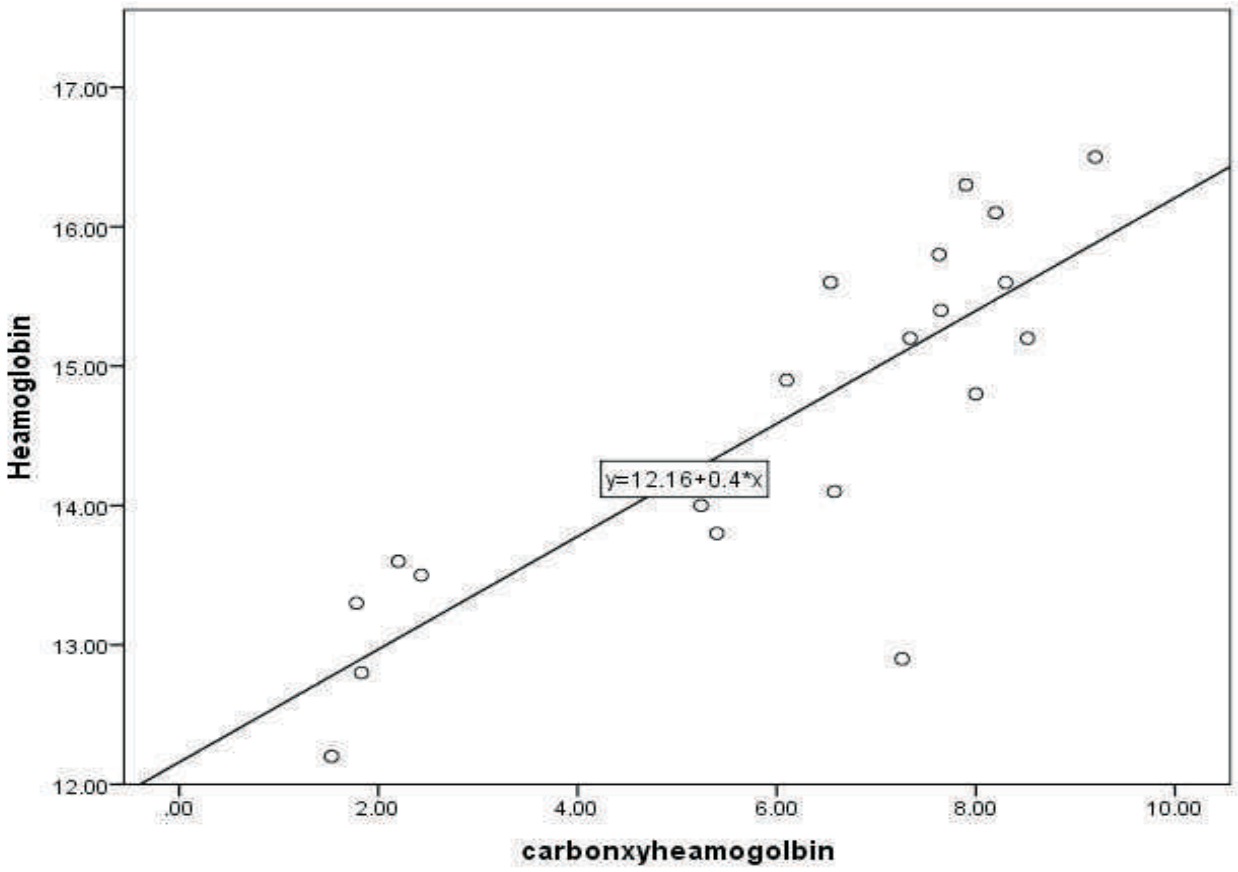

Figure 2: Scatter plot showing the correlation between Carboxyhaemoglobin and Haemoglobin

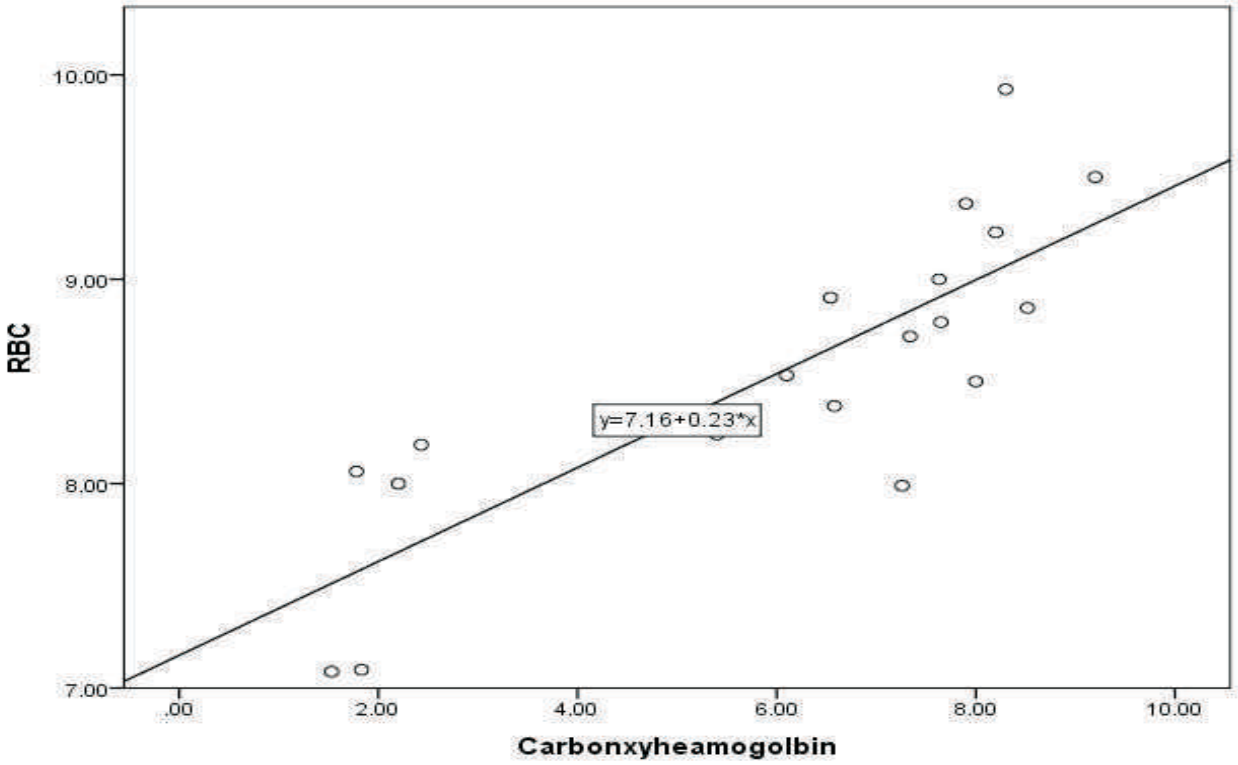

Figure 3: Scatter plot showing the correlation between Carboxyhaemoglobin and RBC

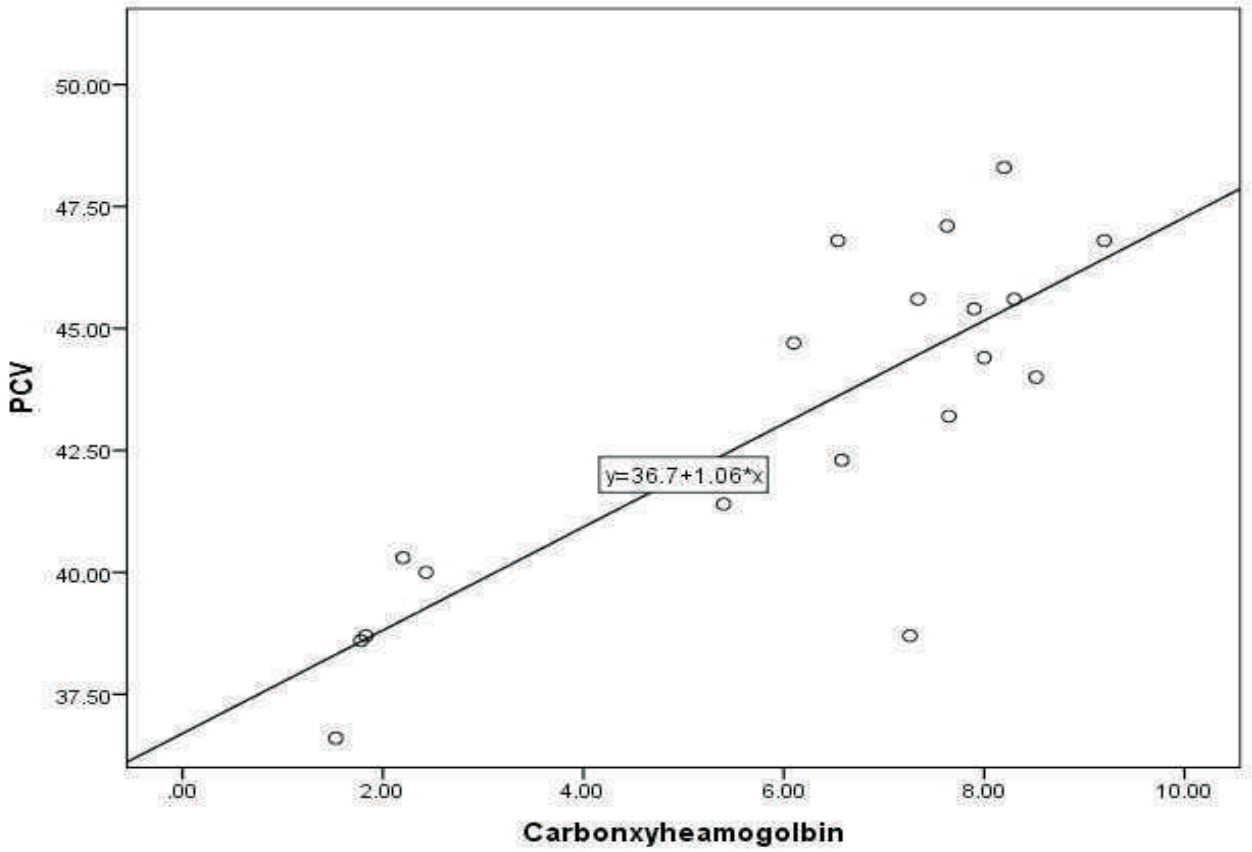

Figure 4: Scatter plot showing the correlation between Carboxyhaeglobin and PCV

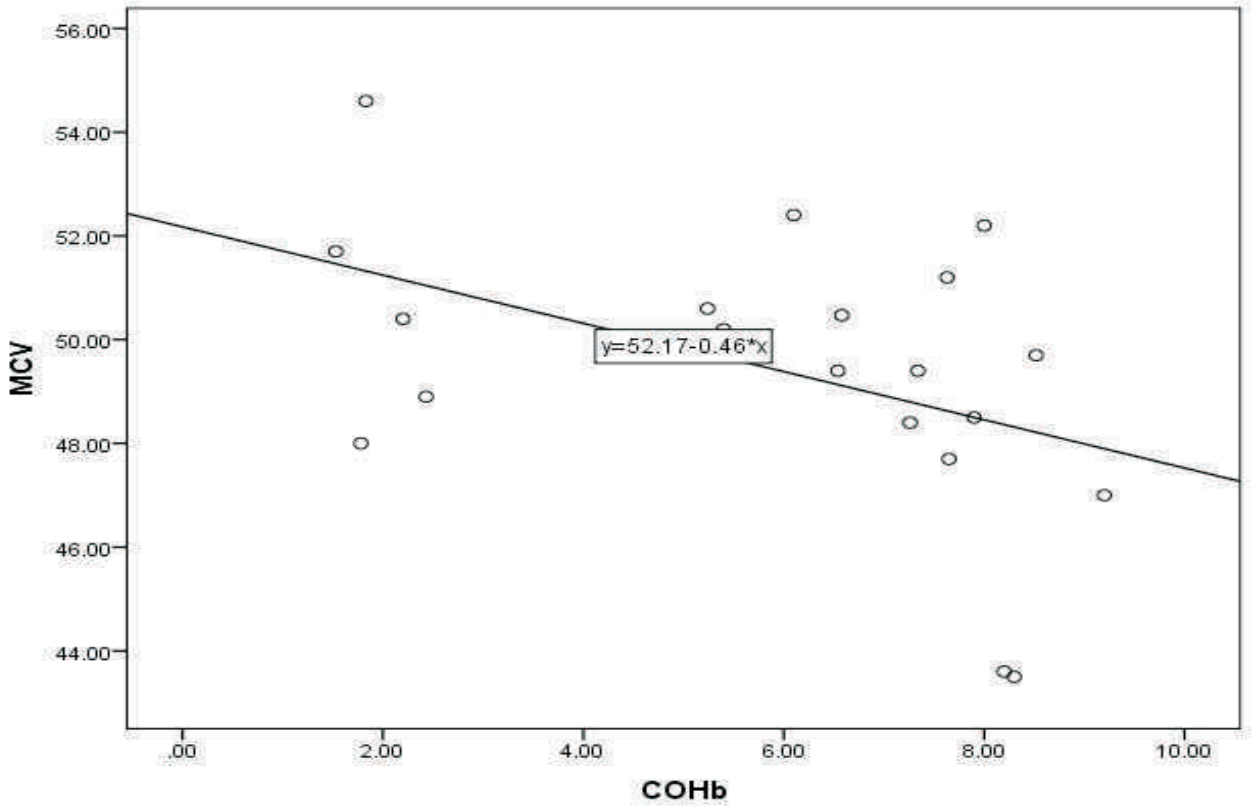

Figure 5: Scatter plot showing the correlation between Carboxyhaemoglobin and MCV

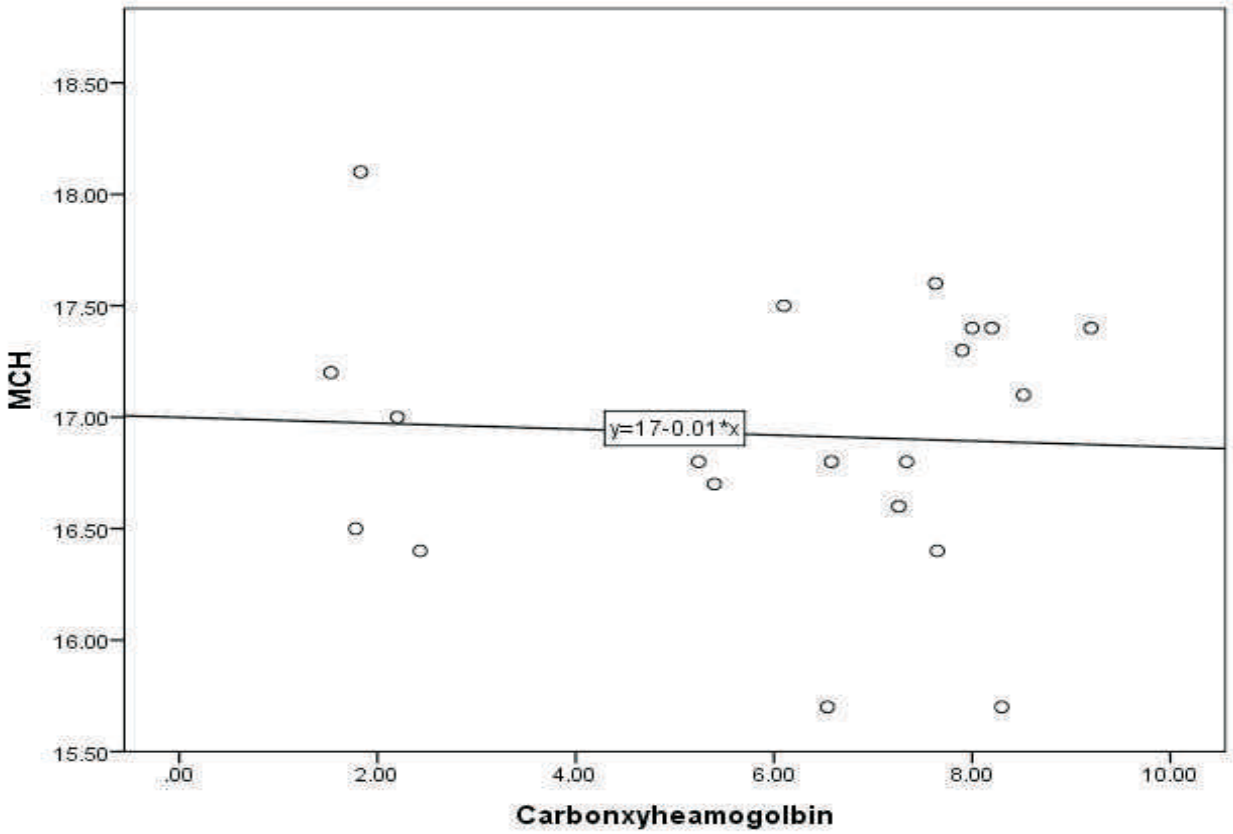

Figure 6: Scatter plot showing the correlation between Carboxyhaemoglobin and MCH

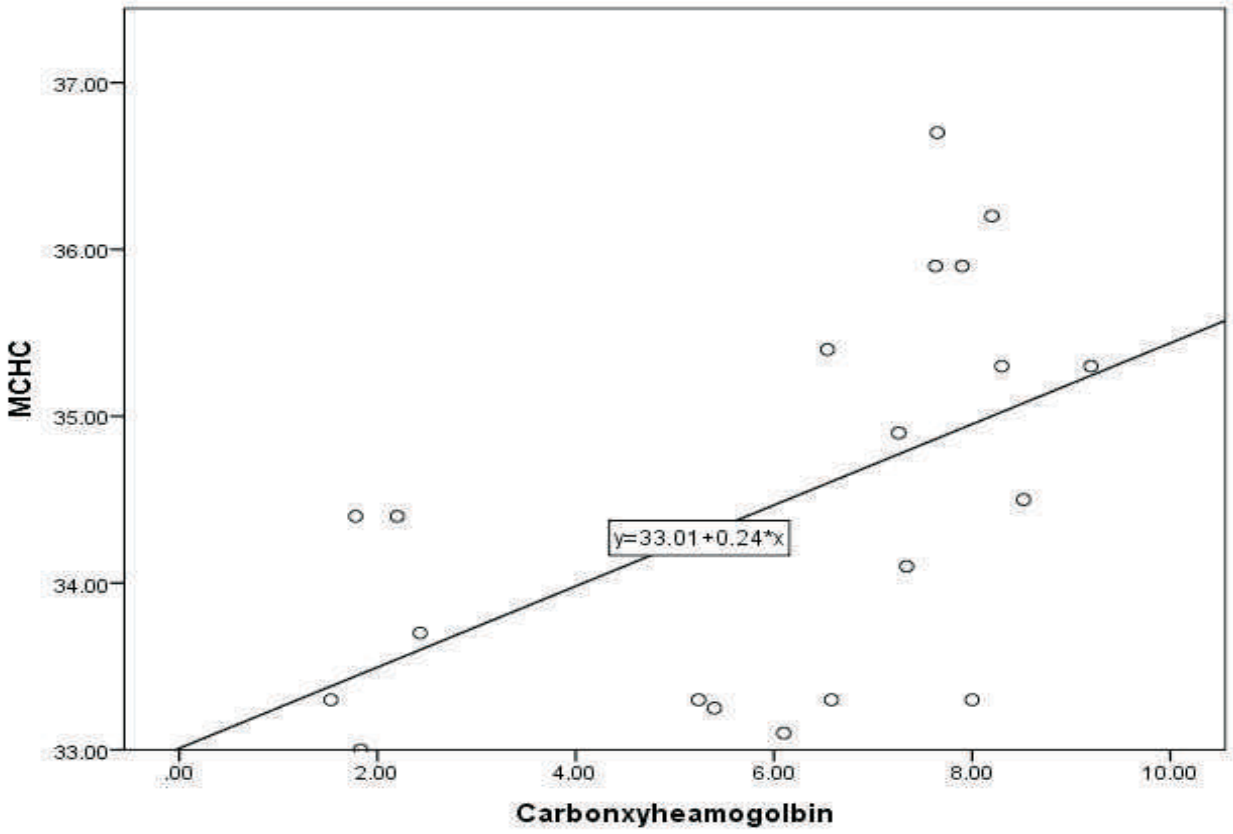

Figure 7: Scatter plot showing the correlation between Carboxyhaemoglobin and MCHC

Discussion

Chronic carbon monoxide (CO) inhalation has long been associated with significant alterations in various haematological parameters, which are pivotal to the oxygen-carrying capacity and overall systemic homeostasis of an organism. The results of this study on Wistar rats highlight the haematological impact of prolonged CO exposure, focusing on haemoglobin (Hb) concentration, red blood cell (RBC) count, packed cell volume (PCV), and carboxyhaemoglobin (COHb) levels.

The present study demonstrated a statistically significant increase in haemoglobin levels with increasing CO exposure durations. Control animals (Group A) had the lowest mean Hb (13.08±0.6 g/dl), while rats exposed to CO for three weeks (Group D) exhibited the highest mean Hb (15.80±0.6 g/dl), with a p-value of <0.001. The pairwise comparison also confirmed significant differences between the control and exposure groups, especially between Groups A and D ($p < 0.001$). These findings align with those of Kato *et al.* (2016), who observed elevated Hb levels in chronic CO exposure due to the body's compensatory mechanism to counteract the reduced oxygen availability, resulting in increased erythropoiesis. This erythropoietic response aims to enhance oxygen transport despite the presence of COHb, which impairs Hb's oxygen-binding capacity.

However, contrasting studies, such as McGrath and Burakoff (2021), have reported that excessive and prolonged CO exposure leads to a decline in Hb levels due to chronic hypoxia, which depletes the bone marrow's ability to sustain erythropoiesis. The difference in findings may relate to variations in CO concentration and exposure periods between studies, suggesting that short-term exposures might increase Hb levels, while long-term exposures could lead to deleterious effects.

A similar pattern was observed for RBC counts, where chronic CO inhalation resulted in a marked increase. Control animals exhibited a mean RBC count of 7.68±0.6×10 /µl, whereas rats exposed for three weeks had significantly elevated RBC counts (9.29±0.5×10 /µl). Statistical analysis revealed a significant difference between Groups A and D ($p < 0.001$), confirming a robust erythropoietic response. This is consistent with findings from a study by Collier *et al*. (2019), where increased RBC production in response to hypoxic conditions induced by CO exposure was observed. The body's attempt to mitigate the reduced oxygen-carrying capacity due to COHb formation leads to erythrocytosis, a compensatory physiological mechanism. In contrast, Yoon *et al.* (2017) observed no significant increase in RBC counts in a similar study, suggesting that RBC levels may stabilize over prolonged CO exposure periods as the body's compensatory mechanisms are overwhelmed. This highlights that CO exposure duration and concentration are crucial factors influencing haematopoietic responses.

Packed cell volume (PCV) also increased significantly with CO exposure, as demonstrated by the mean values ranging from 38.84±1.5% in Group A to 46.44±1.5% in Group C. Notably, the differences between control and exposed groups were statistically significant ($p < 0.001$). This observation aligns with prior research by Ahmed *et al.* (2020), which reported elevated PCV values following chronic CO exposure due to increased erythropoietic activity in response to CO-induced hypoxia. The increase in PCV mirrors the changes in RBC count and Hb concentration, further supporting the idea that CO exposure triggers compensatory haematopoietic responses. However, there are studies such as that by Ghosh and Singh (2018), where PCV levels declined after prolonged exposure to high levels of CO. This suggests that extended exposure could potentially impair the body's ability to produce and maintain adequate RBCs, resulting in a decline in PCV over time.

Interestingly, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) did not exhibit significant changes across the exposure groups, with p-values of 0.166 and 0.926, respectively. This indicates that while CO inhalation influences total RBC count and Hb concentration, it does not substantially affect the size or Hb content of individual red cells within the observed exposure period. These findings are consistent with those of Rai and Agrawal (2019),

who found that MCV and MCH values remain stable during short-term CO exposure. The lack of significant change in these parameters suggests that erythropoiesis triggered by CO exposure primarily affects the quantity, rather than the quality, of RBCs.

On the other hand, mean corpuscular haemoglobin concentration (MCHC) showed a statistically significant increase ($p = 0.007$), particularly between Groups A and D. This suggests that CO exposure may lead to a higher Hb concentration within RBCs, a phenomenon also reported by Diab *et al.* (2022), where MCHC levels increased in response to chronic CO exposure as a compensatory adaptation to hypoxia.

COHb levels, as expected, increased significantly with prolonged CO exposure. The control group had a mean COHb level of 1.95±0.4%, while the group exposed for three weeks exhibited an alarming 8.31±0.6%, with a highly significant p-value of <0.001. COHb formation is a direct consequence of CO binding to haemoglobin, which inhibits the latter's ability to carry oxygen. This study's findings are in line with those of Zwart *et al*. (2020), who also reported increased COHb levels in CO-exposed animals, highlighting the dose-dependent relationship between CO exposure duration and COHb accumulation. As COHb levels rise, oxygen delivery to tissues becomes severely compromised, which may explain the body's compensatory erythropoietic response.

Interestingly, studies like that of Fern *et al*. (2018) emphasize that beyond a certain threshold, elevated COHb levels can no longer be counterbalanced by increased RBC production, leading to tissue hypoxia and subsequent organ damage. This underscores the potential risks associated with chronic CO exposure, especially at higher concentrations.

A strong positive correlation was observed between carboxyhaemoglobin and haemoglobin ($r = 0.823$, $p < 0.001$). This suggests that as carboxyhaemoglobin levels increase, haemoglobin levels also rise. Haemoglobin's affinity for carbon monoxide is well established, with CO forming carboxyhaemoglobin by binding to haemoglobin with a higher affinity than oxygen. This process leads to the competitive displacement of oxygen from haemoglobin, ultimately resulting in elevated carboxyhaemoglobin levels in the blood. Similar positive correlations between carboxyhaemoglobin and haemoglobin have been reported in previous studies. For instance, Tak *et al.* (2022) found that increased CO exposure in experimental animal models leads to elevated haemoglobin concentrations, a compensatory mechanism triggered by hypoxia from CO inhalation (Tak *et al.,* 2022).

A significant positive correlation was also found between carboxyhaemoglobin and red blood cell count ($r = 0.822$, $p < 0.001$). This implies that chronic exposure to CO may stimulate erythropoiesis in response to reduced oxygen-carrying capacity, a consequence of the increased formation of carboxyhaemoglobin. Such an adaptive response has been documented in previous studies, where chronic CO inhalation was associated with an elevated RBC count to counteract the effects of tissue hypoxia. A study by Zhang *et al.* (2021) reported similar findings, indicating that CO exposure enhances erythropoietin production, thus promoting the formation of new red blood cells as a compensatory response to hypoxemia (Zhang *et al.,* 2021).

The study also demonstrated a significant positive correlation between carboxyhaemoglobin and PCV ($r = 0.810$, $p < 0.001$). PCV, a reflection of the total percentage of red blood cells in the blood, similarly increased with rising carboxyhaemoglobin levels. This finding aligns with the compensatory mechanism of increased erythropoiesis in response to chronic CO inhalation. A similar positive relationship between carboxyhaemoglobin and PCV was observed in a study by Jang *et al.* (2019), where chronic CO exposure led to an elevation in haematocrit values in animal models (Jang *et al.,* 2019). The increase in PCV supports the notion that erythropoietic responses to CO-induced hypoxia drive haematological changes.

Interestingly, a significant negative correlation was observed between carboxyhaemoglobin and

MCV (r = -0.446, p = 0.049). This indicates that as carboxyhaemoglobin levels rise, the average volume of red blood cells decreases. This finding suggests that chronic CO exposure may induce microcytic changes in red blood cells, possibly because of altered iron metabolism or oxidative damage induced by CO. A study by Lee et al. (2020) also reported a reduction in MCV in subjects exposed to chronic low-dose CO, attributing it to iron deficiency and disruption in red blood cell maturation (Lee *et al*., 2020).

The correlation between carboxyhaemoglobin and MCH was negative but not significant (r = -0.056, p = 0.813), indicating no substantial relationship between the two variables. MCH reflects the average amount of haemoglobin in each red blood cell. Although the lack of a significant correlation suggests that chronic CO exposure may not affect the haemoglobin content of individual red blood cells, previous research has shown mixed results. Some studies, such as that by Smith *et al*. (2018), reported no significant changes in MCH values following CO exposure, supporting the findings of the current study (Smith *et al*., 2018).

A significant positive correlation was observed between carboxyhaemoglobin and MCHC (r = 0.535, p = 0.015). MCHC represents the concentration of haemoglobin in a given volume of packed red blood cells. The increase in MCHC observed in the current study may reflect alterations in haemoglobin distribution within red blood cells due to CO binding. Increased MCHC has been documented in previous studies as a response to CO inhalation. For example, Anderson et al. (2020) observed a rise in MCHC in rats exposed to chronic CO, suggesting that CO binding to haemoglobin alters the erythrocyte's oxygen-carrying capacity and promotes compensatory changes (Anderson *et al*., 2020).

The results of this study are consistent with the findings of previous research on CO inhalation and its effects on haematological parameters. Chronic CO exposure typically results in elevated levels of carboxyhaemoglobin, reduced oxygen-carrying capacity, and compensatory haematopoietic responses, as indicated by increased haemoglobin, RBC count, and PCV. The significant positive correlations observed in this study between carboxyhaemoglobin and these parameters are in line with previous animal model studies, such as those conducted by Jang *et al.* (2019) and Zhang *et al.* (2021).

However, the negative correlation between carboxyhaemoglobin and MCV, as well as the non-significant relationship with MCH, highlight the complexity of CO's effects on red blood cell morphology and haemoglobin content. These findings are corroborated by studies such as Lee *et al.* (2020), which reported microcytic changes following chronic CO exposure.

Conclusion

The results of this present study indicate that exposure to CO significantly affects various blood parameters. Notably, there was a marked increase in haemoglobin (Hb), red blood cell (RBC) count, packed cell volume (PCV), and carboxyhaemoglobin levels in the CO-exposed groups compared to the control. These changes were statistically significant across the different exposure durations (7, 14, and 21 days). Conversely, the mean corpuscular volume (MCV) showed a significant decrease, while mean corpuscular haemoglobin (MCH) remained relatively stable, and mean corpuscular haemoglobin concentration (MCHC) increased with prolonged exposure. Correlation analysis revealed significant positive correlations between COHb levels and Hb, RBC count, PCV, and MCHC, while a negative correlation was observed with MCV.

Recommendations

1. **Safety Measures**: Implement stringent safety measures and proper ventilation in environments where carbon monoxide is used or produced to minimize exposure and prevent potential health risks.
2. **Monitoring**: Regular monitoring of carboxyhaemoglobin levels in individuals exposed to carbon monoxide is recommended to detect early signs of toxicity and prevent long-term health issues.
3. **Further Research**: Conduct additional studies to explore the mechanisms behind the observed changes in haematological parameters and their potential long-term effects on health. Consider evaluating the

effects in different animal models and at varying levels of exposure.

4. **Public Awareness**: Increase awareness about the dangers of carbon monoxide exposure and promote preventive strategies to safeguard public health, especially in areas with high risk of CO exposure.
5. **Policy Implementation**: Develop and enforce regulations that ensure safe use of carbon monoxide in industrial and domestic settings, including guidelines for maximum allowable exposure levels.

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