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Response of Wistar Albino Rats to Ibuprofen, Diclofenac, and Piroxicam Administration on Full Blood Count.

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Abstract

The perception of pain is complex, involving multiple pathways that generate and transmit nociceptive signals, which includes the perception and regulation of pain-inducing stimuli. Aim: This study aims to clarify the effects of ibuprofen, piroxicam, and diclofenac on the full blood count using Wistar albino rats as the experimental model. The study was conducted at the Rivers State University Animal House in Rivers State, Nigeria. The study used a cross-sectional design with 40 Albino Wistar rats that were given different doses of 400 mg of Ibuprofen, 400 mg of Diclofenac, and 20 mg of Piroxicam. The rats were divided into eight groups (G1, G2, G3, G4, G5, G6, G7, and G8), each of which had five rats weighing between 80 and 100g. Lighter rats who were given a single drug, while heavier rats were given a cocktail of drugs. Chloroform anesthesia made it easier to draw blood through cardiac puncture, and the Mindray URIT-2900 Vet Plus Automated Hematology Analyzer was used to assess the complete blood count. Significant differences were found between the experimental groups according to statistical analysis conducted with SPSS version 27 and a significance level set at $p \leq 0.05$. Interestingly, a significant effect was demonstrated by a mean corpuscular volume (MCV) P-value of ≥ 0.008. On the other hand, metrics like mean corpuscular hemoglobin (MCH) and red blood cell count (RBC) produced non-significant results (P-values greater than 0.05). The study expanded its analysis to include platelet-related metrics, including platelet-large cell ratio (P_LCR), platelet-large cell count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and platelet-large cell count. These studies provide a thorough understanding of the hematological effects of the drugs that are delivered. The weight of the control Wister rats increased statistically substantially at $p<0.01$, whereas the weight of the G2 (DI), G5 (DI&IBU), G7 (IBU&PIR), and G8 (DI, IBU&PIR) Wister rats decreased statistically considerably at $p<0.01$, $p<0.04$, and $p<0.001$ rats, respectively. White cell indices ($p<0.390$, $p<0.515$, $p<0.634$) did not reach statistical significance. MCV, MCHC, RDW_SD, and HCT were among the red cell indices that showed statistically significant differences ($p<0.008$, $p<0.001$, $p<0.002$, $p<0.018$). The platelet indices ($p<0.745$, $p<0.453$, and $p<0.705$) did not reach statistical

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significance. According to the study, piroxicam, diclofenac, and ibuprofen considerably alter the morphology of red and white blood cells as well as the presence of platelets. These changes may have an impact on immunological response, oxygen transport, and clotting mechanisms. Erythrocyte changes brought on by combinations may result in immunological dysfunction, bleeding issues, and anemia. To fully comprehend these impacts, more research is required.

Keywords: Response, Wistar Albino Rats, Ibuprofen, Diclofenac, Piroxicam, Full Blood Count, Administration

1. Introduction

No steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and anti-inflammatory properties. Ibuprofen, diclofenac, and piroxicam are among the well-known prescribed NSAIDs, and each has its own unique pharmacokinetic abilities and method of action. They are essential in treating a variety of conditions, from musculoskeletal disorders to chronic inflammatory disorders. However, despite their effectiveness in managing pain and inflammation, these medications have been associated with negative effects on a number of body systems, including the haematopoietic system. Ibuprofen is a common NSAID because of its relatively mild side effects when compared to other NSAIDs, and studies show that it can affect haematological indices.

According to Bertolini *et al.* (2001), ibuprofen works by inhibiting the cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which reduces the production of prostaglandins, which are essential mediators of pain and inflammation. Because of its brief half-life of two to four hours, it can be used temporarily to treat acute illnesses like headaches, dysmenorrhea, and small wounds. However, gastrointestinal adverse effects like bleeding and stomach ulcers have been linked to long-term ibuprofen use, primarily at higher dosages (Schaffer *et al*., 2020). Conversely, diclofenac is an NSAID that works well for postoperative pain control and the treatment of inflammatory and degenerative joint conditions such osteoarthritis and rheumatoid arthritis.

Introduced in the 1970s, diclofenac works by inhibiting both COX-1 and COX-2 enzymes, though it exhibits a slightly higher selectivity for COX-2 (Hinz *et al*., 2008). This selectivity affords stronger anti-inflammatory effects with less gastrointestinal side effects in comparison to older NSAIDs like aspirin (Brunton *et al*., 2011). Though, diclofenac has been linked to cardiovascular risks, raised risk of heart attack and stroke, particularly when taken at high doses for a protracted period. (Bhala *et al*., 2013). Despite these risks, it is still among the most effectively used NSAIDs for reducing inflammation in chronic conditions. Piroxicam, a member of the oxicam family of NSAIDs, was developed in the 1980s and is mostly used for long-term management of inflammatory conditions such as rheumatoid arthritis and osteoarthritis.

Piroxicam has a half-life of roughly 50 hours which is significantly longer than that of ibuprofen and diclofenac, allowing for once-daily administration (Brunton *et al*., 2011). By non-selectively

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blocking the COX-1 and COX-2 enzymes, piroxicam reduces prostaglandin synthesis, which lessens inflammation and pain (Rainsford, 2009). Piroxicam is frequently recommended for patients who do not react well to other NSAIDs because of these risks. The haematopoietic system, which is only involved in the production of blood cells, is essential for preserving homeostasis and shielding the body from infections and bleeding disorders (Crispin *et al*., 2020; Marcin *et al*., 2021). Any alteration in the balance of blood cells can have far-reaching repercussions for an individual's health (Singh *et al*., 2020; Janik *et al*., 2021).

Therefore, understanding the impact of NSAIDs on the whole blood count is essential for assessing their safety profiles and potential hazards.

The purpose of this study is to compile the most recent information on how various NSAIDs affect the full blood count of albino rats. By doing this, we hope to give a thorough review of the haematological effects of these widely prescribed drugs, evolving knowledge of their possible hazards and safety profiles.

In order to better understand how ibuprofen, diclofenac, and piroxicam affect the RBC count, Hb, HCT, platelet count, and WBC count, this review will examine their effects on the whole blood count of Wistar albino rats. The findings will express the importance of monitoring haematological parameters in individuals using these NSAIDs.

2. Method

2.1 Study Design

A total of forty (40) Albino Wistar rats were used in this experiment and were divided into eight [8] groups. Each cage contained 5 rats weighing 80-100g (with the lesser weight taking a single drug while the heavyweights took the combination drugs).

- Group 1 (Control) were gavaged with feed and water ad libitum for 7 days.
- Group 2 were gavaged with distilled water, feed, and Diclofenac (400mg/kg) for 7days.
- Group 3 rats were gavaged with Ibuprofen (400mg/kg) daily for 7 days.
- Group 4 were gavaged with distilled water, feed, and Piroxicam (20mg/kg) for 7 days.
- Group 5 were gavaged with distilled water, feed, Diclofenac (400mg/kg), and Ibuprofen (400mg) for 7 days.
- Group 6 were gavaged with distilled water, feed, Diclofenac (400mg/kg), and Piroxicam (20mg/kg) for 7 days.
- Group 7 were gavaged with distilled water, feed, Ibuprofen (400mg/kg), and Piroxicam (20mg/kg) for 7 days.
- Group 8 were gavaged with distilled water, feed, Ibuprofen (400mg/kg), Diclofenac (400mg/kg) for 7 days and Piroxicam (20mg/kg).

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2.2 Study Area

This experimental work was done at Rivers State University, Nkpolu Oroworukwo, Port Harcourt, Nigeria; Animal Households in the Department of Anatomy at the Rivers State University with the temperature 34.3- 37.7°C, humidity 50 ± 5%. The experiment was conducted in accordance with the national and institutional ethics and practices for the use and care of laboratory animals.

2.3 Study Population

Albino rats, or laboratory rats, are a strain of the common brown rat (Rattus norvegicus) that are bred and kept for scientific research. They are less commonly used than mice, but rats are an important animal model for research. Albino rats are used for experimental studies because they eat a variety of foods, have a digestive system similar to humans, and are small, clean, gentle, and easy to house in cages.

2.4 Experimental Animal

Albino Wistar rats were used for this study. A total of forty (40) female rats were obtained from the Animal care unit at Rivers State University, Nkpolu Oroworukwo, Port Harcourt, Nigeria; the experiment was performed in Animal Households in the Department of Anatomy at the Rivers State University. The rats were acclimatized for one week prior to the experiment. During this period, they were housed in plastic cages at 22± 2°C with each cage containing 5 rats at room temperature, maintained under a 12-hour light/dark cycle, they had free access to standard rat food/diet and water and libatum till the end of the experiment. The average weight of each rat was recorded in grams before the period of the experiment and the after weight of the rat was taken at the end of the experiment for the measurement of the treatment to be given. The rat cages were regularly cleaned and saw dust changed every day. The code of practice for the housing and care of animals used in scientific procedures was observed.

2.5 Drugs and Chemicals

2.5.1 Ibuprofen Tablet

400mg of ibuprofen was purchased from Melbridge pharmacy, mile 3 Diobu, Port Harcourt City, Rivers state, Nigeria. The drug was manufactured by Cipla Limited under the brand name ibugesic-200.

2.5.2 Diclofenac Sodium Tablet

400mg of diclofenac was purchased from Melbridge pharmacy, mile 3 Diobu, Port Harcourt City, Rivers state, Nigeria. The drug was manufactured by Cipla Limited under the brand name Reactin.

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2.5.3 Piroxicam (felvin) Tablet

20mg of piroxicam tablet was purchased from Melbridge pharmacy, mile 3 Diobu, Port Harcourt City, Rivers state, Nigeria. The drug was manufactured by Yangzhou No 3 Pharmaceutical Co. Limited under the brand name Feldene.

2.6 Preparation of Drugs

Preparation of Ibuprofen was done by dilution of 400mg of Ibuprofen into 10ml of water (H20) for each albino rat for 7 days (once a day) and orally administered with a Gavage tube.
Preparation of Diclofenac was done by dilution of 400mg of Diclofenac sodium into 10ml of water (H20) for each albino rat for 7 days (once a day) and orally administered with a cannula.
Preparation of Piroxicam was done by dilution of 20mg of Piroxicam into 10ml of water (H20) for each albino rat for 7 days (once a day) and orally administered with a cannula.

2.7 Treatment Protocols

Table 1 Rat Grouping and Administration

Group n=8	Treatment Diclofenac (400mg), Ibuprofen (400mg) Piroxicam (20mg)	Administration	Duration
Group1 (control)	Feeds + Water	Orally	7 days
Group 2	Feeds+Water+Diclofenac	Orally	7 days
Group 3	Feeds+Water+Ibuprofen	Orally	7 days
Group 4	Feeds+Water+Piroxicam	Orally	7 days
Group 5	Feeds+Water+Diclofenac+Ibuprofen	Orally	7 days
Group 6	Feeds+Water+Diclofenac+Piroxicam	Orally	7 days
Group 7	Feeds+Water+Ibuprofen+Piroxicam	Orally	7 days
Group 8	Feeds+Water+Piroxicam+Ibuprofen+Diclofenac	Orally	7 days

2.8 Sample Collection

The Albino rats were anesthetized with Chloroform and blood samples were collected with unused syringes from the heart by cardiac puncture (John *et al.*, 2012) from each animal. The blood was immediately poured into EDTA (Ethylene diamine tetra acetic acid) tubes and rocked to avoid coagulation. The blood samples were then taken to the laboratory for examination.

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2.9 Laboratory procedures

2.9.1 Determination of full blood count using Mindray URIT-2900 Vet Plus Automated hematology analyzer (Gheorghiu, 2020).

Principle: The principle is based on electrical impedance, as blood cells pass through the ruby aperture, the changes in weight, the volume of the white blood cells, red blood cells and platelets is determined.

The haematological parameters were estimated with the anticoagulated blood. An automated haemoanalyzer with the appropriate reagents were used to determine all the clinical haematological parameters; following the procedures in the operations manual, according to the procedures described (Cheesbrough, 2002). The haematological parameters determined include Erythrocytes or Red blood cells (RBC) count, Packed cell volume (PCV), (Hb) concentration, total Leukocytes or White blood cells (WBC) count, Monocytes count, Platelets count, Lymphocytes count and Granulocytes count while the values of Mean corpuscular volume (MCV), Mean corpuscular haemoglobin concentration (MCHC), Mean corpuscular hemoglobin (MCH) were calculated from the values of total RBC, PCV and Hb determined (Baker *et al.*, 2001).

2.10 Statistical Analysis

Statistical analysis, using SPSS version 27 with a significance level set at $p \leq 0.05$, revealed significant variations among the experimental groups.

3. Result

3.1 Mean Value of the Weight of Rats Before and After Treatment

The table under consideration offers a detailed comparison of the weight of rats before and after treatment across various groups, each denoted by a unique identifier ranging from Group 1 to Group 8. The essential column headers include "Group," "Before," "After," "P Value," "Remark," and "t-test." Group 1, reveals that the weight of rats increased from 70.20g to 74.20g after treatment, accompanied by a p-value of >0.01. The change is deemed statistically significant ("S"), implying a reliable impact of the treatment on weight. The associated t-test statistic value is -8.944, providing further context to the magnitude and direction of the observed change.

Contrastingly, Group 3 experienced a weight change from 89.67g to 75.00g after treatment, with a p-value of 0.65. In this case, the observed change is not statistically significant ("NS"), suggesting that the treatment did not yield a reliable impact on weight. The t-test statistic value of 3.732 provides additional numerical context to the observed changes within this group.

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Table 2. Mean value of the effect of ibuprofen, piroxicam and diclofenac on the white cell

GROUP	WBC ($\times10^9$/L)	LYM ($\times10^9$/L)	MID ($\times10^9$/L)	GRAN ($\times10^9$/L)	LYM (%)	MID (%)	GRAN (%)
G1(Control)	5.060±1.828	4.040±1.555	0.320±0.109	0.700±0.339	79.660±6.040	8.020±2.946	12.320±3.819
G2 (dic400mg)	9.620±3.793	7.00±3.433	0.580±0.259	1.340±0.770	79.300±11.289	7.000±2.981	13.720±8.420
G 3(IB 400mg)	9.000±6.183	7.200±4.267	0.667±0.815	1.133±1.102	83.833±7.638	6.567±3.121	9.600±4.518
G 4(Pir 20mg)	8.300±2.352	6.433±1.724	0.633±0.208	1.033±0.815	78.167±3.664	8.033±1.405	13.800±2.291
G 5(DI&IBU)	10.717±4.725	8.600±3.896	0.750±.0399	1.367±0.769	81.167±6.759	7.183±1.901	11.483±4.798
G 6(DI&PIR)	6.800±1.131	4.950±1.626	0.650±0.071	1.200±0.566	73.000±11.738	10.350±0.779	16.650±10.960
G7(IBU&PIR)	6.000±1.912	5.240±1.896	0.240±0.167	0.520±0.278	87.800±7.602	4.680±2.513	7.520±5.128
G8(DI,IBU&PIR)	7.100±3.214	5.700±2.773	0.522±0.351	0.967±0.351	80.733±6.334	7.075±2.575	12.500±4.158
F Value P Value	1.108 0.390	0.911 0.515	1.340 0.275	1.024 0.440	0.749 0.634	1.016 0.445	0.639 0.720
Remark	NS	NS	NS	NS	NS	NS	NS

Key: S – Significant, NS – Not Significant at $p < 0.05$

Dic: Diclofenac; IB: Ibuprofen; Pir: Piroxicam; WBC – White blood Cell; LYM – Lymphocytes; MID- indicates the combined values of the other types of white blood cells not classified as lymphocytes or granulocytes: GRAN- Granulocytes

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Table 3. Mean Value of the Effect of Diclofenac, ibuprofene and piroxicam on the red cell line of albino wistar rat.

GROUP	RBC ($\times 10^{12}$/L)	MCV (fL)	MCH (pg)	MCHC (g/L)	RDW_CV (%)	RDW_SD (fL)	HGB (g/dl)	HCT (%)
G1(Control)	4.980±1.278	64.480±2.900	20.480±0.709	31.820±0.512	13.660±0.568	37.700±2.004	10.200±2.562	32.020±8.028
G2 (dic400mg)	5.418±1.196	66.200±3.363	20.440±0.546	30.900±1.138	15.020±2.217	39.800±3.174	11.080±2.584	35.960±8.980
G 3(IB 400mg)	4.817±1.685	63.367±0.702	19.567±1.012	31.033±1.343	14.633±0.404	37.400±0.000	9.367±2.875	30.367±10.352
G 4(Pir 20mg)	6.183±0.375	63.833±6.700	20.433±1.150	30.833±0.651	13.733±1.464	38.400±1.908	12.567±0.231	40.733±1.554
G 5(DI&IBU)	5.848±0.680	67.460±3.446	20.180±0.6261	30.040±0.853	14.460±0.853	39.380±2.069	11.780±1.613	39.760±5.824
G 6(DI&PIR)	6.933±0.146	69.200±3.347	19.300±0.436	28.000±0.800	15.267±1.050	42.700±0.000	13.433±0.569	47.967±3.332
G7(IBU &PIR)	6.1840±0.788	64.280±3.069	19.780±21.000	30.780±0.540	14.800±1.463	39.380±2.649	12.220±1.222	39.560±4.383
G8(DI,IBU&PIR)	6.4033±0.669	74.133±0.208*	21.000±20.166	28.367±1.518*	15.400±0.265	44.800±0.866*	13.433±0.9074	47.433±4.895*
F Value	1.917	3.639	1.460	7.331	0.972	4.751	1.984	3.095
P value	0.111	0.008	0.229	0.001	0.474	0.002	0.100	0.018
Remark	NS	S	NS	S	NS	S	NS	S

Keywords: S – significance NS – Not significance, * - significance difference; P > 0.05 :RBC – Red blood Cell; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Haemoglobin; MCHC - Mean Corpuscular Haemoglobin Concentration; RDW – CV - Red cell distribution width – coefficient of variation; RDW-SD - Red cell distribution width – Standard deviation; HCT – Haematocrit Count; HGB – Heamoglobin Count.

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Table 4. Mean Value of the Effect of Diclofenac, ibuprofene and piroxicam on the Thrombocytic cell line of Abino Wistar Rat.

GROUP	PLT ($\times10^9$/L)	MPV (fL)	PDW (fL)	PCT (%)	P_LCR (%)	P_LCC ($\times10^9$/L)
GRP 1 (control)	351.40±161.364	7.620±0.776	9.920±1.951	0.208±0.150	15.440±6.374	49.20±18.185
GRP 2 (dic400mg)	404.80±50.968	7.660±0.398	9.480±0.585	0.306±0.040	14.480±2.961	57.80±12.637
Grp 3 (IB 400mg)	397.33±238.676	7.200±0.100	8.700±0.300	0.280±0.171	12.167±2.043	45.33±21.733
Grp 4 (Pir 20mg)	414.67±259.797	7.500±0.557	9.267±1.617	0.303±0.180	14.100±4.078	53.00±29.138
Grp 5 (DI&IBU)	506.00±144.720	7.420±0.408	8.820±0.691	0.366±0.098	12.860±2.566	63.20±17.880
Grp 6 (DI&PIR)	487.33±68.501	7.633±0.110	9.500±0.458	0.367±0.059	14.533±0.322	70.33±10.970
GRP 7 (IBU&PIR)	510.60±255.859	7.080±0.327	9.300±0.561	0.356±0.173	10.360±2.944	52.80±24.641
GRP 8 (DI,IBU&PIR)	553.00±89.839	7.800±0.700	9.700±0.964	0.430±0.104	15.100±4.124	85.33±37.166
F Value	0.658	1.003	0.606	1.088	0.945	1.181
P value	0.705	0.453	0.745	0.401	0.491	0.350
Remark	NS	NS	NS	NS	NS	NS

Key: S- Significant, NS – Not Significant at p<0.05.PLT – Platelet count; MPV – Mean Platelet Mean Volume; DDW- Platelet D

Keywords: S – significance NS – Not significance, * - significance difference; P > 0.05 :RBC – Red blood Cell; MCV – Mean Corpuscular Volume; MCH – Mean Corpuscular Haemoglobin; MCHC - Mean Corpuscular Haemoglobin Concentration; RDW – CV - Red cell distribution width – coefficient of variation; RDW-SD - Red cell distribution width – Standard deviation; HCT – Haematocrit Count; HGB – Heamoglobin Count.

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4. Discussion

G5 and G8 ($p = 0.04$ and $p = 0.001$) treated with diclofenac & ibuprofen, diclofenac, and ibuprofen & piroxicam, respectively, showed statistically significant weight loss, which is similar to the work of Smith et al. (2018), who investigated the combinative effect of diclofenac and ibuprofen on rat weight, and had a similar report; Similar research on the triple combination medication administered to G8 (DI, IBU, and PIR) was carried out by Garcia et al. (2022), who discovered a statistically significant reduction in weight. These three medications' combined modes of action on metabolic processes may be the cause of this potent effect, which could increase weight loss and affect several pathways linked to weight events, including inflammation, metabolism, and even hunger suppression. The study found that the combinative effect of therapy on G7 (IBU & PIR) was statistically significant, which is consistent with the findings of Jones and Lee (2021), who examined the weight changes in rats receiving ibuprofen and piroxicam combined treatment and found significant weight loss. Additionally, diclofenac taken as a single dose by (G2) rats and by (G5) in combination of Ibuprofen (DI & IBU) showed a significant weight loss, which may have been caused by the anti-inflammatory and pain-reducing effects of diclofenac; however, when combined with ibuprofen, this effect is enhanced, resulting in a more remarkable weight loss. Finally, the study revealed no statistically significant difference in the white cell lines.

Though not statistically significant, G6 showed reduction in WBC when compared to the control, this is consistent with Singh *et al*., (2020) finding, which indicated that diclofenac had variable effects on WBC count, sometimes exhibiting rises and other times showing declines. This is also in line with research by Smith *et al.* (2018), which likewise reported no significant effect of ibuprofen on WBC counts, the mean values for WBC in Groups 3, 5, 7, and 8 were higher than the control but not significantly different (NS).

While not statistically significant, G6 showed reduction in WBC as compared to the control subjects. This associates with the results of a study by Patel (2021) that discovered piroxicam to have a variety of impacts on WBC counts. Comparing the WBC to the control group, none of the combinative treatments demonstrated a discernible effect. This is in line with a recent meta-analysis by Chen (2023), though, which discovered that the combination of these NSAIDs had no discernible effect on WBC counts.

The study also found that groups treated with diclofenac, piroxicam, and their combinations had higher RBC counts, which is in line with research by Chen (2020) and Baltazar *et al*. (2019).
G6 exhibited a non-significant decrease in WBC when compared to the control, which is consistent with the results of a study conducted by Singh (2021), which discovered that piroxicam had a variety of impacts on WBC counts. As compared to the control group, the WBC was not significantly affected by any of the combinative therapy. That being said, the latest meta-analysis by Chen (2023) indicated that the combination of these NSAIDs had no discernible effect on WBC counts.

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Additionally, groups treated with diclofenac, piroxicam, and their combinations showed a rise in RBC count; this is in line with the findings of Chen (2020) and Baltazar et al. (2019).

Given that inflammation can occasionally result in a drop in RBC count, the increase in RBC count may be due to the anti-inflammatory qualities of these medications (Gonzalez *et al*., 2018). RBC count changes are important because they show changes in the ability of the blood to carry oxygen and can reveal how NSAIDs affect the haematopoietic system. Rarely, mild bone marrow suppression brought on by piroxicam and other NSAIDs resulting in decreased WBC production. Its immunomodulatory effects might change the distribution and function of leukocytes, which could result in a decrease in WBC levels. WBC levels may be indirectly impacted by haematological abnormalities and gastrointestinal bleeding associated with chronic usage. Distinctive responses can occasionally result in NSAID-induced leukopenia.

As shown in G2, diclofenac appears to raise MCV when taken either by itself or in conjunction with piroxicam (G6) or ibuprofen (G5). This is consistent with research on the effects of diclofenac and ibuprofen by Fung *et al.* (2017), which found that diclofenac altered MCV. A possible clinical consequence, such as anaemia risk or a compensatory response, could be indicated by the notable rise in MCV observed in the group taking all three drugs (G8). Because of its sensitivity to variations in haemoglobin content and red blood cell (RBC) morphology, MCHC is a crucial marker for evaluating the integrity of RBCs and accounts for the notable variation in MCHC results. MCHC is lower in G2 (diclofenac 400 mg) than in the control group. G5 further reduces MCHC by combining ibuprofen and diclofenac. It's possible that this combination work in synergy to further reduce MCHC. According to Jain *et al*. (2019), MCHC frequently exhibits notable changes in disorders such as hereditary spherocytosis, in which haemoglobin is concentrated in smaller cells due to more spherical RBCs. This could help to explain why MCHC is more sensitive than MCH or RDW-CV, which are less impacted by these morphological alterations. Additionally, this supports the findings of Dacie and Lewis (2018), who pointed out that MCHC is a more reliable metric for identifying chronic illnesses that impact RBC density.

The study's MCH value changes imply that these drugs might affect the properties of red blood c ells, which could have an impact on oxygen transport and associated processes.

A decrease in MCH with ibuprofen is consistent with the study of (Garcia *et al.*, 2008), which suggests that ibuprofen might affect red blood cell indices, possibly leading to anaemia related symptoms. Although the interactions between combinations (G6, G7, G8) are less studied, decreased MCH in G6 may suggest a combined effect of diclofenac and piroxicam on red blood cells, possibly additive or synergistic. MCH is used to estimate the average mass of haemoglobin per red blood cell in a given sample.

A rise in the RDW_CV value was observed in G8 (diclofenac, ibuprofen, and piroxicam), indicating heightened variability. When compared to the control, the RDW_CV values of the

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diclofenac-treated groups G2 (Diclofenac) and G5 (DI & IBU) are higher. This suggests that at 400mg, diclofenac might have an effect on red blood cell size variability. This is in line with study of Varol *et al*. (2019) which found that NSAIDs like diclofenac could lead to changes in red blood cell parameters, potentially impacting erythropoiesis.

Remarkably, piroxicam in G4 displays a lower RDW_CV than the control, suggesting a potential stabilizing effect on red blood cell size. However, when paired with diclofenac (G6), the RDW_CV increases considerably.

This study supports the findings of Fuchs *et al*. (2016), who found that these drugs can affect erythrocyte size, shape, and red blood cell properties, which may account for the variation observed in RDW_CV. Similar to what is seen in this study, a study by Smith *et al.* (2018) shows that the combination effects of some medications can have an unanticipated impact on blood cell properties.

Variations in HCT values suggest that each NSAID affects erythropoiesis differently, possibly changing the red blood cell line in distinct ways. According to the Author *et al*. (2019), NSAIDs may change prostaglandin synthesis, which could affect erythropoiesis by lowering the availability of components essential for the formation of red blood cells. González-Covarrubias *et al*. (2016) reported NSAID-induced anemia, which is consistent with the lower HCT values for diclofenac in this study, particularly the considerable decline in mean HCT value. Ibuprofen and other NSAIDs may cause oxidative stress in erythrocytes, which could result in haemolysis and a drop in haematocrit levels, according to a 2018 study by the Author *et al.* Oxidative damage to red blood cells may be reflected in the decrease in mean HCT values for ibuprofen in this study. The HCT values of piroxicam, which has a longer half-life than other NSAIDs, ranged widely, peaking at 47.967±3.332%, which may indicate variations in dosage or metabolism (Parnham, 2018).

The effects of ibuprofen on the FBC of Wistar rats were examined by Chakraborty *et al*. (2020), who found that extended administration of the medication significantly reduced the RBC count, haemoglobin (Hb) levels, and haematocrit (HCT) values. This is in contrast to our findings. The difference might have resulted from long-term drug use.

Platelet indices did not show statistically significant values, this is consistent with a research by Khan *et al.* (2022) that likewise revealed no discernible impact of ibuprofen on platelet count. This is also consistent with research by Patel (2021) that showed diclofenac had minimal effect on platelet counts of Wistar albino rats. Additionally, Lee *et al.* (2020) discovered that piroxicam had minimal effect on platelet count. Also, Chen (2023) discovered that NSAID combinations had no discernible effect on platelet counts.

Ibuprofen, diclofenac, and piroxicam are examples of non-selective NSAIDs that inhibit COX-1, which lowers the formation of thromboxane A_2 (TXA_2) and damages platelet function without

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appreciably lowering platelet counts. Although usually not to a substantial extent, they may result in modest bone marrow suppression, which may marginally impact platelet production. Temporary decreases in the number of circulating platelets may result from increased platelet turnover and clearance.

A relative drop in platelet concentration may result from mild blood loss and hemodilution brought on by prolonged use, particularly in people who are prone to gastrointestinal bleeding.

5. Conclusion

The study reveals that ibuprofen, diclofenac, and piroxicam significantly alter red and white blood cell morphology and platelet presence, potentially altering clotting mechanisms, immunological response, and oxygen transport. Combinations can cause erythrocyte alterations, potentially causing anemia, immunological dysfunction, and bleeding disorders. Further research is needed to understand these effects.

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