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Haematological safety of salbutamol, montelukast, prednisolone, and their combinations in ovalbumin-induced asthmatic rats

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ABSTRACT

Background: The mainstay drugs for asthma, salbutamol, montelukast, and prednisolone, are often prescribed together, but their haematological effects vary across different studies. **Objective:** In this study, we looked at their individual and combined effects on the circulating cellular profile in experimental asthma. **Methods:** Sixty-four female Sprague-Dawley rats were randomly assigned to eight groups: a negative control, an ovalbumin (OVA) positive control, and OVA-asthmatic animals treated orally with salbutamol (1 mg/kg), montelukast (10 mg/kg), prednisolone (3 mg/kg), or their combinations. Asthma was induced using OVA (1 mg i.p.) and AIOH₃ (20 mg i.p.) sensitisation on days 1 and 7, followed by a 28-day intranasal aerosol challenge with 1% (w/v) OVA. Leukocyte, erythrocyte, and platelet indices were measured in whole blood using an automated haematology analyzer. Tukey's post hoc test was used to compare the data after one-way ANOVA. **Results:** Prednisolone increased WBC compared with the positive control (11.80 ± 0.98 vs $7.25 \pm 0.61 \times 10^3/L$; $p < 0.05$) and MID-cell count compared with the negative control (25.94 ± 2.27 vs 15.22 ± 1.55 %; $p < 0.05$). Prednisolone/montelukast reduced lymphocytes compared with the negative control (53.31 ± 5.57 vs 72.73 ± 3.39 %; $p < 0.05$), whereas salbutamol/prednisolone increased granulocytes compared with the positive control ($p < 0.05$). RBC and haemoglobin increased with prednisolone and salbutamol/prednisolone, while platelet count increased only with prednisolone/montelukast ($p < 0.05$). MCH, RDW, MPV, PDW, PCT and P-LCR remained unchanged ($p > 0.05$). **Conclusion:** The haematological footprint of these antiasthmatics was largely dictated by prednisolone's leukocytotic and erythrostimulatory properties, while salbutamol and montelukast were largely neutral. This suggests their co-administration carries no disproportionate haematological risk; larger, longer-term studies are needed to confirm this.

Keywords: Asthma, Haematological Indices, Salbutamol, Montelukast, Prednisolone.

INTRODUCTION

Inflammatory diseases of the airways, such as asthma, are characterized by bronchial hyperresponsiveness and luminal obstruction, but their pathophysiology extends beyond the respiratory compartment and causes measurable systemic problems. Extrapulmonary manifestations include altered circulating cellular profiles, including leukocytosis, eosinophilia, variable erythrocytic indices, and platelet activation [1-3]. The full blood count is an accessible and sensitive mirror of systemic inflammatory load [1,3]. The diagnostic and prognostic value of these haematological readouts is now well established, with full blood count parameters and their derived inflammatory ratios shown to differentiate asthma phenotypes and track disease severity and outcome [4,5]. This kind of inflammatory index has been shown to be a cost-effective surrogate of asthmatic inflammatory status in resource-constrained settings, including much of sub-Saharan Africa [6].

In the stepwise therapeutic ladder, asthma is managed with a combination of several mechanistically distinct drug classes. The short-acting agonist salbutamol relaxes airways smooth muscle via cyclic adenosine monophosphate and exerts further systemic metabolic effects after absorption [7]. The cysteinyl leukotriene receptor antagonist montelukast attenuates leukotriene-driven inflammation and bronchoconstrictor cascades and reduces eosinophilia in the blood and sputum [8,9].

Montelukast, a cysteinyl leukotriene receptor antagonist, attenuates the leukotriene-driven inflammatory and bronchoconstrictor cascade and characteristically reduces blood and sputum eosinophilia [8,9]. Prednisolone, a systemic glucocorticoid, suppresses inflammation through broad genomic and non-genomic actions and constitutes the mainstay of exacerbation management. Because these agents are commonly co-prescribed, the systemic consequences of their combined administration, rather than of each in isolation, are of direct clinical relevance.

Each of these drug classes is known to engage the haematological system through actions that are mechanistically separable from its airway pharmacology. As a result of demargination and delayed neutrophil apoptosis, glucocorticoids cause neutrophilic leukocytosis, redistributive lymphocytopenia, and stress erythropoiesis by signaling glucocorticoid receptors in erythroid progenitor cells [10-13]. According to human evidence, β_2 -adrenergic stimulation modifies leukocyte trafficking and platelet behavior, but not the erythroid lineage [14,15]. Beyond blocking canonical receptors, montelukast has off-target purinergic effects on platelet P2Y₁₂ receptors, which can attenuate platelet activation and platelet-eosinophil interactions. This is relevant to allergic airway disease, where platelets are active participants [16-19]. Despite this substantial body of single-agent data, it remains unclear how these drugs interact with the circulating cellular profile, whether they act additively, synergistically, or antagonistically.

Using ovalbumin-induced rodent models of allergic asthma, we can examine systemic drug effects against a defined asthmatic background, replicating the cardinal immunological and inflammatory features of asthma. Thus, the present study tested the effects of salbutamol, montelukast, and prednisolone, given individually or combined, on ovalbumin-sensitive rats' leukocyte, erythrocyte, and platelet counts. This study aims to determine how these widely used agents behave systemically and whether co-administration imposes any disproportionate haematological risks.

MATERIAL AND METHODS

Chemicals and Reagents

All chemicals and reagents used were of analytical grade and obtained from reputable suppliers in India and China. Ovalbumin (product code P0010-80, CAS 9006-59-1) and aluminium hydroxide (product code 00910, CAS 21645-51-2) were obtained from LOBA CHEMIE.

Ethical Approval and Animal Welfare

This research was conducted in strict accordance with the international standards for the care and use of laboratory animals articulated by the National Research Council [20]. The experimental protocol received formal approval from the University of Benin College of Medical Sciences Research Ethics Committee (approval reference CMS/REC/2024/570), and all procedures were performed with due regard for the minimisation of animal suffering.

Experimental Design

Sixty-four (64) female Sprague-Dawley rats, weighing between 180 and 250 g, were obtained from the Department of Anatomy, University of Benin. The animals were housed in a climate-controlled environment with unrestricted access to standard rodent chow and clean drinking water. A fourteen-day acclimatisation period preceded the commencement of the experimental protocol to permit physiological adaptation to the housing conditions. Following acclimatisation, the rats were randomly allocated into eight groups (n = 8 per group). The study was executed over a total period of seven weeks, comprising two weeks of adaptation, one week of sensitisation, and four weeks of concurrent ovalbumin (OVA) challenge and pharmacological treatment. The groups were constituted as follows:

- Group 1 (Negative control): neither asthma-induced nor treated.
- Group 2 (Positive control): OVA-induced asthma; left untreated.
- Group 3: OVA-induced asthma plus salbutamol (1 mg/kg, p.o.).
- Group 4: OVA-induced asthma plus montelukast (10 mg/kg, p.o.).
- Group 5: OVA-induced asthma plus prednisolone (3 mg/kg, p.o.).
- Groups 6-8: OVA-induced asthma treated with drug combinations at the doses specified above, salbutamol/prednisolone (Group 6), salbutamol/montelukast (Group 7), and prednisolone/montelukast (Group 8).

Asthma Induction and Pharmacological Intervention

Allergic asthma was established in Groups 2-8 using an ovalbumin protocol adapted from Aloamaka and Nzopotam [21]. Sensitisation was achieved on days 1 and 7 by intraperitoneal (i.p.) injection of 1 mg OVA (Nanjing Duly Biotech) together with 20 mg aluminium hydroxide [Al(OH)₃; LOBA Chemie] suspended in 0.9% normal saline. Commencing on day 14, the sensitised animals entered a 28-day challenge phase consisting of 15-min exposures to 1% aerosolised OVA administered twice weekly. The negative control received normal saline in place of OVA at each corresponding time point. All therapeutic agents were administered orally throughout the 28-day challenge period.

Blood Sample Collection

At the conclusion of the experimental period, the animals were euthanised by inhalation of chloroform fumes within an enclosed glass chamber. Immediately thereafter, whole blood was obtained by cardiac puncture and dispensed into sterile tubes containing dipotassium ethylenediaminetetraacetic acid (K₂-EDTA) as an anticoagulant. Each tube was gently inverted several times to ensure homogeneous mixing and to preclude clot formation, and samples were processed for haematological analysis without undue delay.

Determination of Haematological Indices

For enumerating cellular elements, an automated haematology analyser operated on the principle of electrical impedance (Coulter principle) was utilized to determine the complete blood count (CBC). Haemoglobin concentration was quantified photometrically using cyanide-free lysing. Further, the instrument produced a three-part leukocyte differential, dividing the total white blood cell population into lymphocytes, mid-range cells (MID; comprising monocytes, eosinophils, and basophils), and granulocytes. Before each analytical run, the analyser was calibrated and its performance verified against commercial quality-control material in accordance with the manufacturer's specifications, and EDTA-anticoagulated whole blood was analysed within 2 h of collection to preserve sample integrity.

For each specimen, the following parameters were measured or derived automatically: the total white blood cell count (WBC) together with the absolute lymphocyte, MID-cell, and granulocyte counts; the red blood cell count (RBC), haemoglobin concentration (Hb), haematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and red cell distribution width expressed both as standard deviation (RDW-SD) and as coefficient of variation (RDW-CV); and the platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and platelet large-cell ratio (P-LCR).

Statistical Analysis

In accordance with standard reporting practices, all results are expressed as mean $\pm$ standard error of the mean (SEM). Data were

analysed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons between group means. Statistical computations were performed using GraphPad Prism (version 10.0.3), with statistical significance accepted at the 95% confidence level ($p < 0.05$).

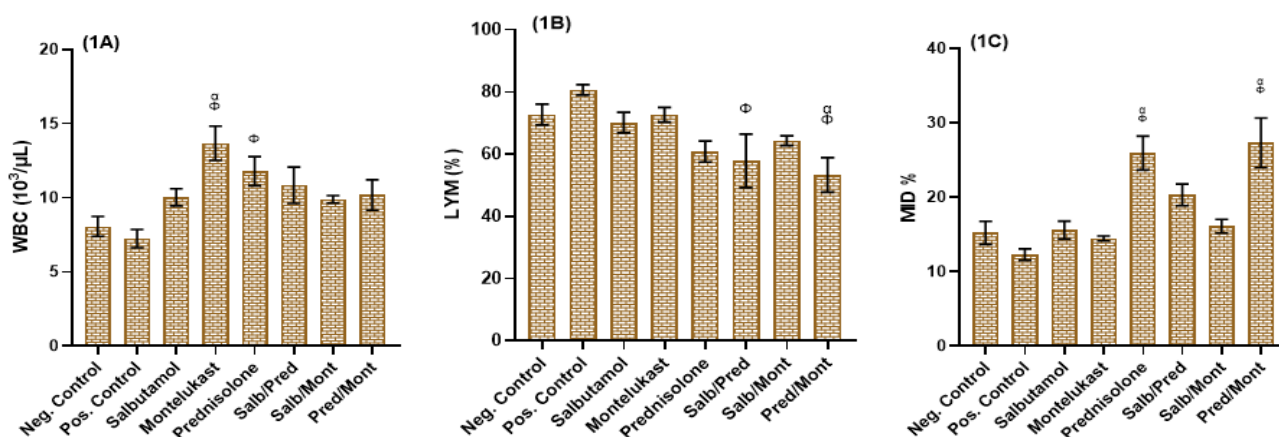
RESULTS

For the haematological parameters, the montelukast-treated group exhibited a significant elevation of the white blood cell (WBC) count relative to the negative control ($p < 0.05$), whereas no significant differences were observed in the positive control, salbutamol-, prednisolone-, salbutamol/prednisolone-, salbutamol/montelukast-, and prednisolone/montelukast-treated groups relative to the negative control ($p > 0.05$). However, the prednisolone-treated group displayed a significant elevation in the WBC count relative to the positive control ($p < 0.05$). The prednisolone/montelukast-treated group demonstrated a significant reduction of the lymphocyte count relative to the negative control ($p < 0.05$), while no significant differences were observed in the positive control, salbutamol-, montelukast-, prednisolone-, salbutamol/prednisolone-, and salbutamol/montelukast-treated groups relative to the negative control ($p > 0.05$). In contrast, lymphocyte count was significantly increased in the prednisolone-treated group compared with the positive control ($p < 0.05$). Analysis of MID cell count revealed significant increases in both the prednisolone-treated and prednisolone/montelukast-treated groups compared with the negative control ($p < 0.05$), whereas the positive control, salbutamol-, montelukast-, salbutamol/prednisolone-, and salbutamol/montelukast-treated groups did not differ significantly from either the positive or negative control groups ($p > 0.05$). Granulocyte count did not differ significantly among any of the treatment groups when compared with the negative control ($p > 0.05$); nevertheless, the salbutamol/prednisolone-treated group exhibited a significant increase relative to the positive control ($p < 0.05$).

Analysis of erythrocytic indices revealed significant alterations in selected parameters following treatment with salbutamol, montelukast, prednisolone, and their combinations. Regarding red blood cell (RBC) counts, a significant elevation was observed in the prednisolone-treated and salbutamol/prednisolone-treated groups relative to the negative control ($p < 0.05$); conversely, no significant variance was noted across the remaining treatment groups ($p > 0.05$).

Similarly, haemoglobin concentration was significantly elevated in the prednisolone-treated and salbutamol/prednisolone-treated groups compared with the negative control ($p < 0.05$), while the remaining treatment groups did not differ significantly from the negative control ($p > 0.05$). With respect to haematocrit (HCT) values, a significant increase occurred solely in the prednisolone-treated group relative to the negative control ($p < 0.05$), with no corresponding alterations noted in the other experimental cohorts ($p > 0.05$). Regarding mean corpuscular volume (MCV), significant elevation occurred within the prednisolone/montelukast-treated group compared to the negative control ($p < 0.05$); in contrast, no significant deviations were detected across the remaining experimental cohorts ($p > 0.05$). A similar trend was observed for mean corpuscular haemoglobin concentration (MCHC), which was significantly elevated in the prednisolone/montelukast-treated group ($p < 0.05$), whereas the remaining groups showed no significant changes compared with either control group ($p > 0.05$). In addition, mean corpuscular haemoglobin (MCH) showed no significant difference across the groups compared with the positive and negative control groups ($p > 0.05$). Furthermore, red cell distribution width expressed as standard deviation (RDW-SD) and coefficient of variation (RDW-CV) did not differ significantly among any of the experimental groups when compared with either the positive or negative control groups ($p > 0.05$).

In the experimental groups, assessment of platelet indices demonstrated limited treatment-related alterations. A significant increase in platelet count was observed in the prednisolone/montelukast-treated group compared with the negative control ($p < 0.05$), whereas no significant differences were observed in the positive control, salbutamol-, montelukast-, prednisolone-, salbutamol/prednisolone-, and salbutamol/montelukast-treated groups relative to either the positive or negative control groups ($p > 0.05$). Mean platelet volume (MPV) did not differ significantly among any of the experimental groups when compared with either the negative or positive control groups ($p > 0.05$). Similarly, platelet distribution width (PDW), plateletcrit (PCT), and platelet large cell ratio (P-LCR) showed no statistically significant differences across all treatment groups relative to both control groups ($p > 0.05$). Collectively, these findings indicate that, although combined prednisolone/montelukast treatment increased platelet count, platelet morphology and volume-related indices remained largely unaffected by asthma induction and subsequent pharmacological interventions.



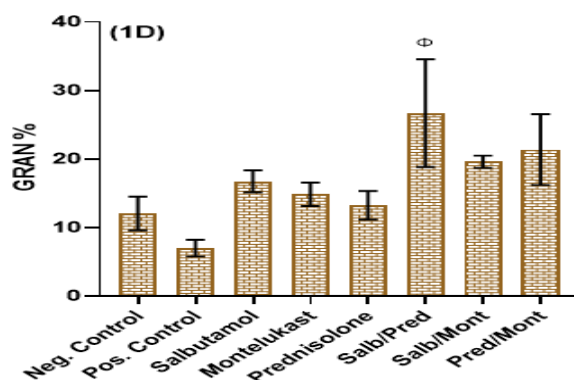


Figure 1: Effect of salbutamol, montelukast, prednisolone, and their combinations on (1A) white blood cell, (1B) lymphocyte, (1C) MID-cell, and (1D) granulocyte counts in ovalbumin-induced asthmatic rats. Data are presented as mean $\pm$ SEM (n = 4). α p < 0.05 versus negative control; Φ p < 0.05 versus positive control

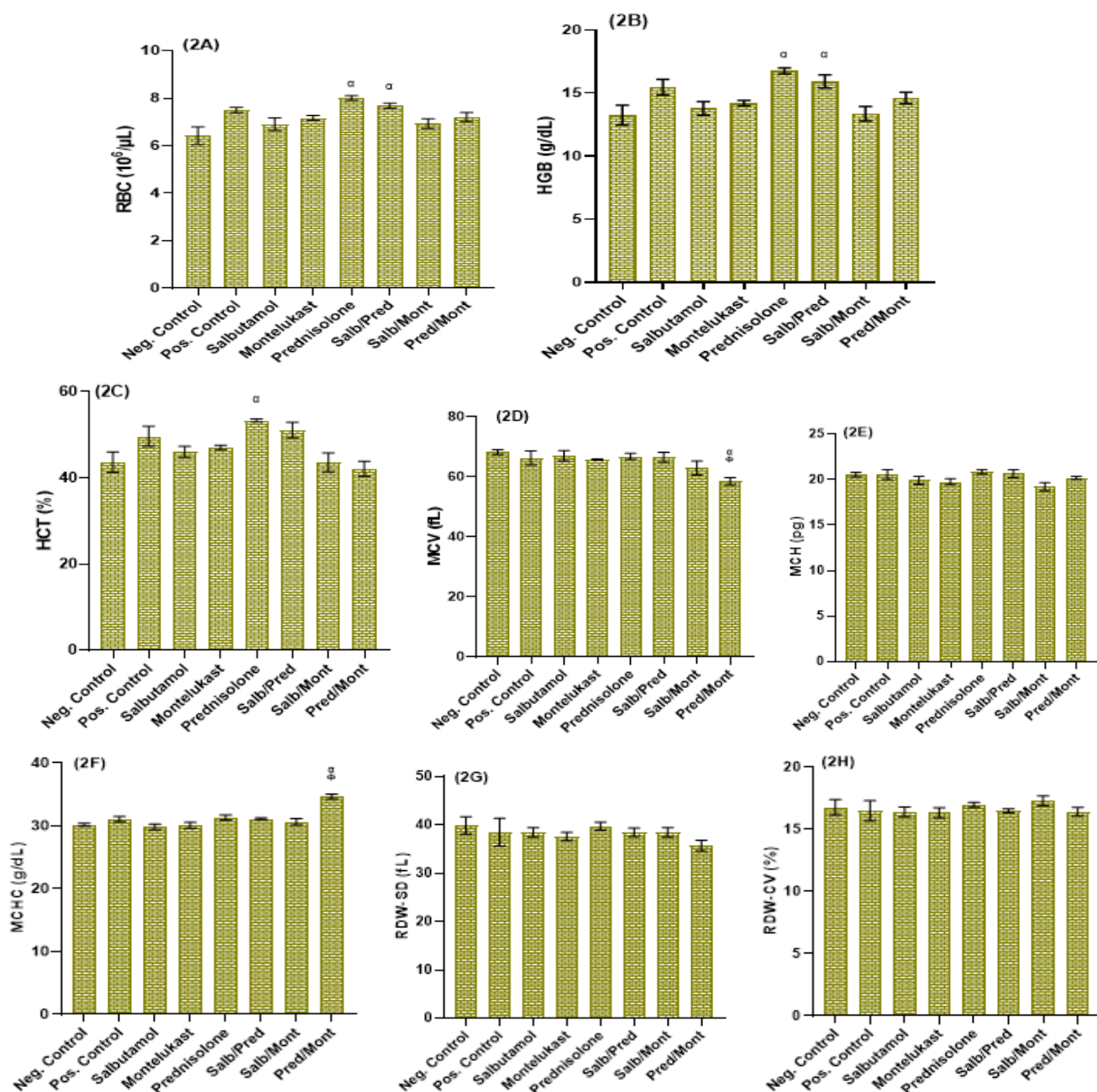


Figure 2: Effect of salbutamol, montelukast, prednisolone, and their combinations on erythrocytic parameters in ovalbumin-induced asthmatic rats. (2A) red blood cell count, (2B) haemoglobin concentration, (2C) haematocrit, (2D) mean corpuscular volume, (2E) mean corpuscular haemoglobin, (2F) mean corpuscular haemoglobin concentration, (2G) red cell distribution width-standard deviation (RDW-SD), and (2H) red cell distribution width-coefficient of variation (RDW-CV). Data are presented as mean $\pm$ SEM (n = 4). α p<0.05 versus negative control; Φ p<0.05 versus positive control

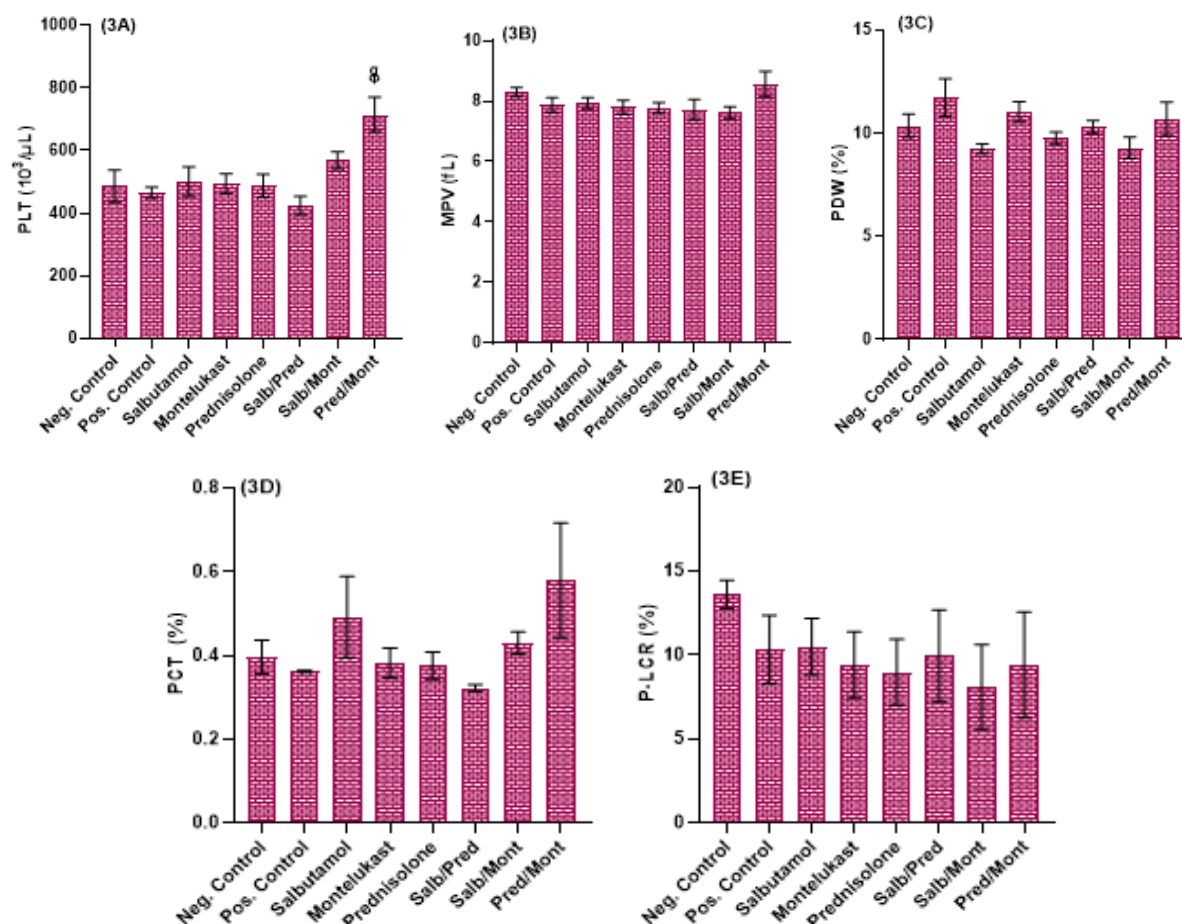


Figure 3: Effect of salbutamol, montelukast, prednisolone, and their combinations on platelet indices in ovalbumin-induced asthmatic rats. (3A) Platelet count, (3B) mean platelet volume (MPV), (3C) platelet distribution width (PDW), (3D) plateletcrit (PCT), and (3E) platelet large cell ratio (P-LCR). Data are presented as mean ± SEM (n = 4). $\alpha p < 0.05$ versus negative control; $\Phi p < 0.05$ versus positive control

DISCUSSION

In addition to the airways, the haematological compartment provides a sensitive and integrative window into systemic consequences of antiasthmatic pharmacotherapy, as it registers perturbations in leukocyte trafficking, erythroid output, and megakaryocyte–platelet kinetics that extend far beyond the airways. An examination of the circulating cellular profile within the present ovalbumin-induced asthmatic model revealed a coherent and biologically interpretable pattern in which changes were overwhelmingly governed by prednisolone-containing regimens, whereas salbutamol and montelukast were comparatively neutral except when they appeared to enhance responses induced by glucocorticoids. Consequently, this hierarchy of effects recapitulates the canonical systemic pharmacology of the three drug classes and, importantly, indicates that their co-administration does not cause disproportionate haematological disturbance within the temporal and dosing framework examined.

Among the leukocyte indices, prednisolone increased the total white blood cell count as well as the MID-cell fraction, confirming the well-established ability of glucocorticoids to induce neutrophilic leukocytosis. A constellation of distributional mechanisms is involved in this response rather than enhanced granulopoiesis. This includes demarginating the intravascular granulocyte pool, accelerating neutrophil egress from bone marrow, slowing transendothelial migration into peripheral tissues, and attenuating neutrophil apoptosis [11,12,22]. Interestingly, the leukocytotic signature occurred primarily against the positive control and not the negative control, which is instructive as it situates the glucocorticoid effect against the altered baseline leukocyte dynamics of the untreated asthmatic comparator. In controlled human exposures to prednisolone, a dose-dependent modulation of leukocytes has been documented [23,24]. The

concomitant reduction in lymphocyte counts within the prednisolone/montelukast group, referenced against the negative control, is similarly consistent with glucocorticoid-induced lymphocytopenia. The phenomenon is primarily attributed to transient redistribution of lymphocytes into extravascular compartments rather than overt cytotoxicity [12,25]. The seemingly paradoxical elevation of lymphocytes in the prednisolone group relative to the positive control group is, therefore, best construed in relative terms, reflecting a disturbance in the leukocyte equilibrium of the asthmatic comparator rather than a primary lymphoproliferative effect of the drug.

A significant increase in granulocyte counts was observed in the salbutamol/prednisolone group when compared to the positive control, raising the possibility of a relationship between β_2 -adrenoceptor agonism and corticosteroid action. Although salbutamol exerts comparatively modest direct effects upon circulating neutrophils and is notably less effective than long-acting congeners at suppressing neutrophil reactivity *in vitro* [26], β_2 -adrenergic stimulation is recognised to mobilise margination-prone granulocyte pools and to promote transient neutrophilia *in vivo* [15,27]. Combined with the corticosteroid-mediated prolongation of neutrophil survival, such mobilization provides a plausible mechanistic explanation for the additive granulocytosis observed during combination therapy. In contrast, the elevation of the total white blood cell count in the monotherapy group was unexpected, as cysteinyl leukotriene receptor antagonists are typically associated with attenuation rather than augmentation of circulating inflammatory cells when antagonism occurs; it has been shown repeatedly that montelukast can diminish both blood and sputum eosinophilia in asthmatic subjects [8,9]. It is prudent to interpret this discordant observation with caution. As indicated by reports that short-term montelukast administration in rodents perturbs haematological parameters in directions not always predicted by its airway pharmacology [28,29], this may reflect biological

variability or a transient compensatory leukocyte response rather than a reproducible pharmacodynamic effect. However, the modest group size must also be considered.

A coherent erythrostimulatory signature emerged within the prednisolone and salbutamol/prednisolone groups, in which red blood cell count and haemoglobin concentration were significantly elevated, accompanied by a rise in haematocrit under prednisolone monotherapy. These findings align with the established role of glucocorticoids in promoting stress erythropoiesis, in which glucocorticoid receptor signalling sustains the self-renewal and proliferation of early erythroid progenitors while delaying their terminal maturation, thereby expanding the erythroid compartment [10,13,30,31]. The synergy of glucocorticoid receptor activation with hypoxia-inducible and metabolic signalling pathways, and the erythrocytosis observed in states of endogenous glucocorticoid excess, lend further mechanistic weight to this interpretation [32–35], as does the proposed retardation of erythrophagocytosis under sustained corticosteroid exposure [36]. Tellingly, the erythroid response under combination was confined to the prednisolone-containing arm; that salbutamol contributed no independent erythroid signal is consistent with the substantial body of human evidence demonstrating that inhaled or systemic β_2 -agonist administration, even at supratherapeutic doses, leaves red cell count, haemoglobin, and related indices essentially unaltered and does not furnish an erythropoietic stimulus [14]. The discrete increases in mean corpuscular volume and mean corpuscular haemoglobin concentration, restricted to the prednisolone/montelukast group, alongside the preservation of mean corpuscular haemoglobin and red cell distribution width across all groups, indicate that these interventions modulated erythroid output without disturbing the morphological integrity or homogeneity of the circulating erythrocyte population.

Platelet indices were mostly refractory to pharmacological manipulation, except for a spike in platelet count in the prednisolone/montelukast group, while mean platelet volume, platelet distribution width, plateletcrit, and the platelet large-cell ratio remained statistically indistinguishable. According to longitudinal studies [37,38], corticosteroids have negligible quantitative effects on platelet number under standard dosing, have a modest effect on platelet reactivity, and at most, cause modest changes in mean platelet volume rather than a wholesale shift in platelet number. The increase in count with prednisolone and montelukast may reflect changes in megakaryocytic maturation kinetics and thrombopoietic signaling in the progenitor pool [39]. The relative quiescence of the platelet compartment is itself noteworthy given the well-documented participation of platelets in allergic airway disease, in which platelet activation, recruitment to the lung, and contribution to bronchial hyperresponsiveness and airway remodelling are firmly established [17], and given the reported capacity of montelukast to attenuate platelet activation and platelet–eosinophil aggregation through cysteinyl leukotriene receptor blockade and off-target purinergic actions [16,18,19,40]. Asthma induction and subsequent interventions altered platelet morphology and volume-related parameters only marginally, while leaving the megakaryocyte-platelet axis largely intact.

These observations acquire their fullest meaning when set against the recognised systemic haematological footprint of asthma itself, which encompasses leukocytosis, variable erythrocytic indices, and platelet activation, and which has been documented in diverse populations, including West African cohorts [1,3,5,6]. Considering this disturbed baseline, the combination regimens tend to be additive, rather than synergistic or antagonistic, so co-administration of salbutamol, montelukast, and prednisolone doesn't make haematological derangements worse than just glucocorticoids. The data show that prednisolone has the most haematological signature among the antiasthmatics examined, whose leukocytotic and erythrostimulatory actions are comparable to glucocorticoids systemically. The

circulating cellular profile is comparatively neutral with salbutamol and montelukast unless they augment prednisolone-driven changes.

CONCLUSION

In this ovalbumin-induced asthmatic model, antiasthmatic therapy's haematological footprint was dominated by prednisolone, which evoked leukocytotic and erythrostimulatory changes consistent with glucocorticoid pharmacology, whereas salbutamol and montelukast remained largely neutral except when augmenting these effects. The combinations proved additive rather than synergistic, suggesting that co-administration carries no disproportionate haematological risk, pending confirmation in larger cohorts with extended dosing.

Author Contributions

AEOO and EFO contributed to the conceptualization and design of the study and to data acquisition. AEOO conducted the literature review and performed the statistical analysis. Both authors took part in the interpretation of the results and the preparation of the manuscript. AEOO acts as guarantor of the manuscript. Both authors read and approved the final version submitted for publication.

Data Availability Statement

The data that support the findings of this study are available and will be made available upon request.

Use of AI in Drafting of Manuscript

During the preparation of this work, the author(s) used Jenni AI, ChatGPT, and Grammarly in order to improve the clarity and quality of written communication. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of Interest

The authors declared no conflict of interest.

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