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Hematological variables and electrolytes experience toxicological changes on combined exposure to Aluminum and Beryllium

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ABSTRACT

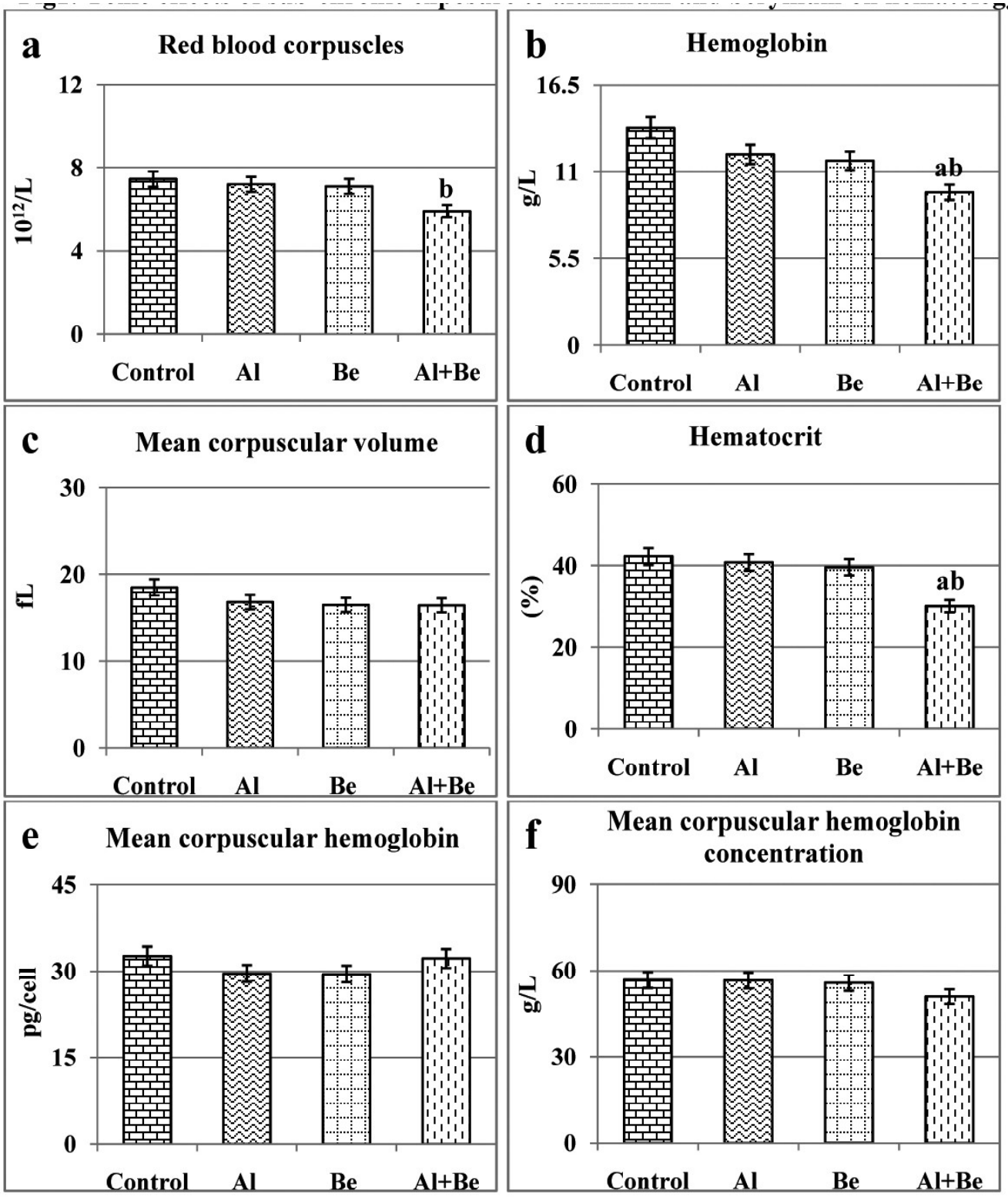
Aluminum (Al) and Beryllium (Be) are light metals, widely used across various sectors. The present study was conducted to investigate toxic effects of Al and Be alone and their combination on hematology and electrolytes in female albino rats. Rats were administered with aluminum nitrate 6.5 mg/kg, *i.p.* and beryllium nitrate 1 mg/kg, *i.p.* for continuous 28 days followed by rest for 07 days. On 36th day, animals were euthanized; blood was collected through retro-orbital venous sinus for hematology and electrolytes. The findings revealed alterations in RBCs, WBCs, Hb, PLT, MCV, HCT, PLCR, MCH, MCHC, PCT and MPV. Significant variations in Na^+, K^+, Cl^- and iCa^{2+} ions were noted in electrolytes in serum. Thus, it can be concluded that individual and combined exposure to Al and Be exert toxic effects by remarkable alterations in hematology and electrolytes; however, combined exposure imposes more pronounced toxic effects.

Figures : 03 References : 34 Table : 00
KEY WORDS : Aluminum, Beryllium, Electrolyte, Hematology

Introduction

Metal pollution is the introduction of toxic elements into the environment through natural and anthropogenic activities that lead adverse effects on living organisms[12]. This poses health problems to humans by disrupting normal physiological functions. Occupational sources of metal exposure include coal mining activities, metallurgy, nuclear power plants, pesticides, smelting and fertilizers industries, which impose significant health risks to the workers and population surviving near these industrial areas[13]. At one side, Pb, Hg, Cd, and As *etc.*, are among the most commonly released heavy metals due to anthropogenic activities and induce severe toxicity among humans. These metals enter the body *via* inhalation, ingestion and dermal contact and generate reactive oxygen species (ROS), suppress antioxidant enzymatic functions, disturb protein functioning, impair enzymatic activities, and alter DNA molecules and their effects[16]. On the other hand, Aluminum (Al) and Beryllium (Be) are light metals, widely used in aerospace, spacecrafts, electronics, nuclear industry and metallurgy from where these are released into the environment[29,30]. Aluminum generally accumulates in vital organs, inhibits enzymatic activities, disturb cellular metabolism by passing through blood-brain barrier[2], leads to neurotoxicity, hemo-toxicity and immune dysfunctions[22]. Beryllium produces toxicity, particularly by affecting lungs to cause chronic beryllium disease (CBD)[14], strongly immuno-toxic[5], alters blood profile[5], suppresses antioxidant enzymes and accumulates in liver, kidney and brain to cause organ toxicity[18,19,20].

Use of Al and Be in various technological purposes and combustion of coal during many industrial activities poses risk of exposure to Al and Be to human and animals both. Thus, it seems essential to study toxic consequences after combined exposure to Al and Be



Data are presented as mean ± SE (n=6); [a]Control vs Al, Be, Al+Be at P≤ 0.01; [b]Control vs Al, Be, Al+Be at P≤ 0.05; [@]significant for ANOVA

Parameters	RBC	Hb	MCV	HCT	MCH	MCHC
F Variance	3.836[@]	7.844[@]	1.308	8.049[@]	1.117	0.983

Fig. 1 : Toxic effects of sub-chronic exposure to aluminum and beryllium on hematology

and establish a multisystem toxicity model for combination of Al and Be. Workers are prone to be co-exposed to both Al and Be, making the study of their combined toxicity environmentally and occupationally relevant.

Thus, this investigation aimed to evaluate sub-chronic toxicity, induced after individual and co-exposure to Al and Be in rats considering hematology and serum electrolytes.

Materials and Methods

Ethical approval and animal maintenance

Animal experiments were conducted in accordance with the guidelines of CPCSEA and experimental design was approved by the institutional animal ethics committee (CPCSEA/GO/Re/S/06). Healthy female Wistar rats (10-12 weeks old having 160±10g body weight) were housed under standard husbandry conditions in cleaned and disinfected polypropylene cages. They were provided standard pelleted rat feed obtained from Akhoorath Ventures Pvt. Ltd., Dehradun, Uttarakhand, India and free access to drinking water.

Experimental design

Aluminum nitrate [$Al(NO_3)_3$] was dissolved in distilled water making up doses of 6.5 mg/5 ml/kg and administered through *i.p.* route[1]. Beryllium nitrate [$Be(NO_3)_2$] was dissolved in distilled water making up doses of 1 mg/5 ml/kg and administered intraperitoneally (i.p.)[33]. Experimental design was as following:

Group 1: Received vehicle 5 ml/ kg, *i.p.* for continuous 28 days and considered as control.

Group 2: Received $Al(NO_3)_3$ 6.5 mg/kg, *i.p.* for continuous 28 days.

Group 3: Received $Be(NO_3)_2$ 1 mg/kg, *i.p.* for continuous 28 days.

Group 4: Received combination of $Al(NO_3)_3$ (6.5mg/kg, *i.p.*) and $Be(NO_3)_2$ (1mg/kg, *i.p.*) for continuous 28 days.

Animals from all the groups were administered vehicle orally for next 07 days. On 36th day, animals were subjected to mild ether anesthesia. Blood samples from all the animals were collected in EDTA coated tubes for hematology and in another set of regular glass vials to isolate serum for electrolyte analysis.

Hematology and electrolyte analysis

Hematology included RBCs, WBCs, platelet (PLT), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet large cell ratio (PLCR), platelet large size ratio (PLSR), mean platelet volume (MPV) and procalcitonin (PCT) was carried out using biogeny fully automatic bonavera count hematology analyzer. Serum electrolytes, including Sodium ions (Na^+), potassium ions (K^+), chloride ions (Cl^-), and ionized calcium (Ca^{2+}) were analyzed using sens-e-lyte ARK diagnosis ISE electrolyte fully automatic analyzer as per manufacturer's instructions.

Statistical analysis

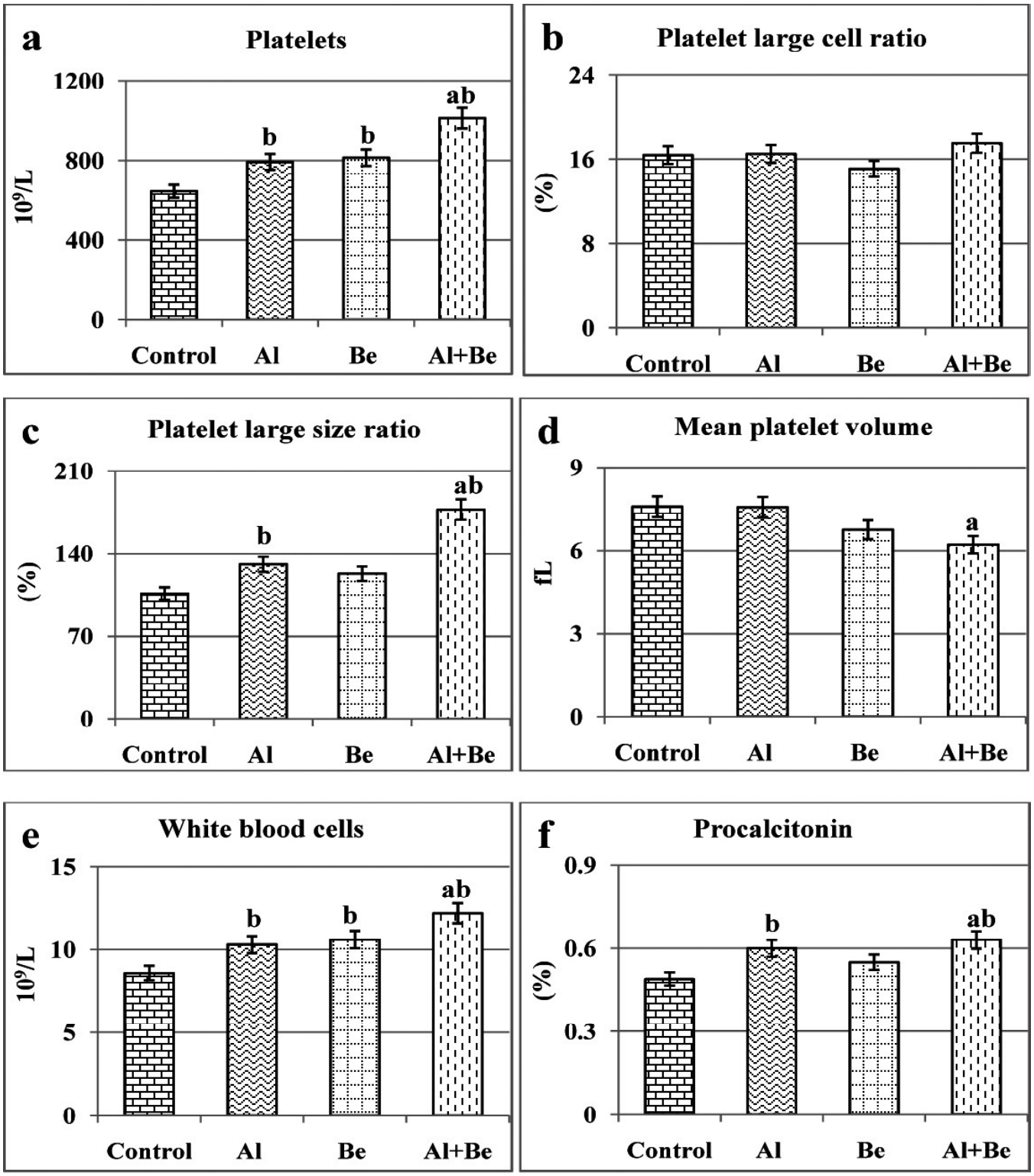
Results were expressed as mean ± SE (n = 6) and statistically analyzed through one-way analysis of variance (ANOVA) followed by student's t-test to determine the significant differences between two groups at $P \leq 0.01$ and $P \leq 0.05$[31].

Results and Discussion

Hematology

Fig. 1 (a-f) illustrates toxic consequences after exposure to Al, Be and its combination on RBCs, Hb, MCV, HCT, MCH and MCHC. Combined exposure to Al and Be elicited significant decrease in RBCs, Hb and HCT as compared to individual exposure to Al and Be ($P \leq 0.01$; $P \leq 0.05$). These effects could be due to Al induced ROS, which initiated peroxidation of RBC membrane lipids, resulting in increased membrane fragility and hemolysis[28]. Exposure to Al disturbed iron metabolism and activity of erythropoietin, thereby declined the production of RBCs in bone marrow[7,8]. The Al^{3+} competes with Fe^{3+} at transferrin binding sites, decreasing its availability for hemoglobin synthesis and ultimately lowering HCT levels[24]. On the other hand, Be^{2+} forms complexes with proteins, triggered autoimmune hemolysis, and suppressed bone marrow formation leading to declination in RBCs, hemoglobin and hematocrit levels[21]. Thus, dual interference of Al and Be in iron metabolism and heme synthesis enzymes markedly reduced RBCs, hemoglobin, and hematocrit. No statistical difference was found in MCV, MCH and MCHC levels.

Fig. 2 (a-f) demonstrates levels of PLT, PLCR, PLSR, MPV, WBCs, and PCT. The PLT and WBCs showed significantly increased level after exposure to Al and Be individually as well as in combination of Al and Be when compared to control at $P \leq 0.01$ and $P \leq 0.05$. The PLSR and PCT revealed significantly increased level in Al and combination of Al and Be group at $P \leq 0.05$, whereas combination of Al and Be showed significant difference at $P \leq 0.01$. Significant fall was noticed in MPV in combination of Al and Be group at $P \leq 0.01$. No significant alteration was noticed in any group in case of PLCR. Accumulation of Al could suppress



Data are presented as mean ± SE (n=6); [a]Control vs Al, Be, Al+Be at P≤0.01; [b]Control vs Al, Be, Al+Be at P ≤ 0.05; [@]significant for ANOVA

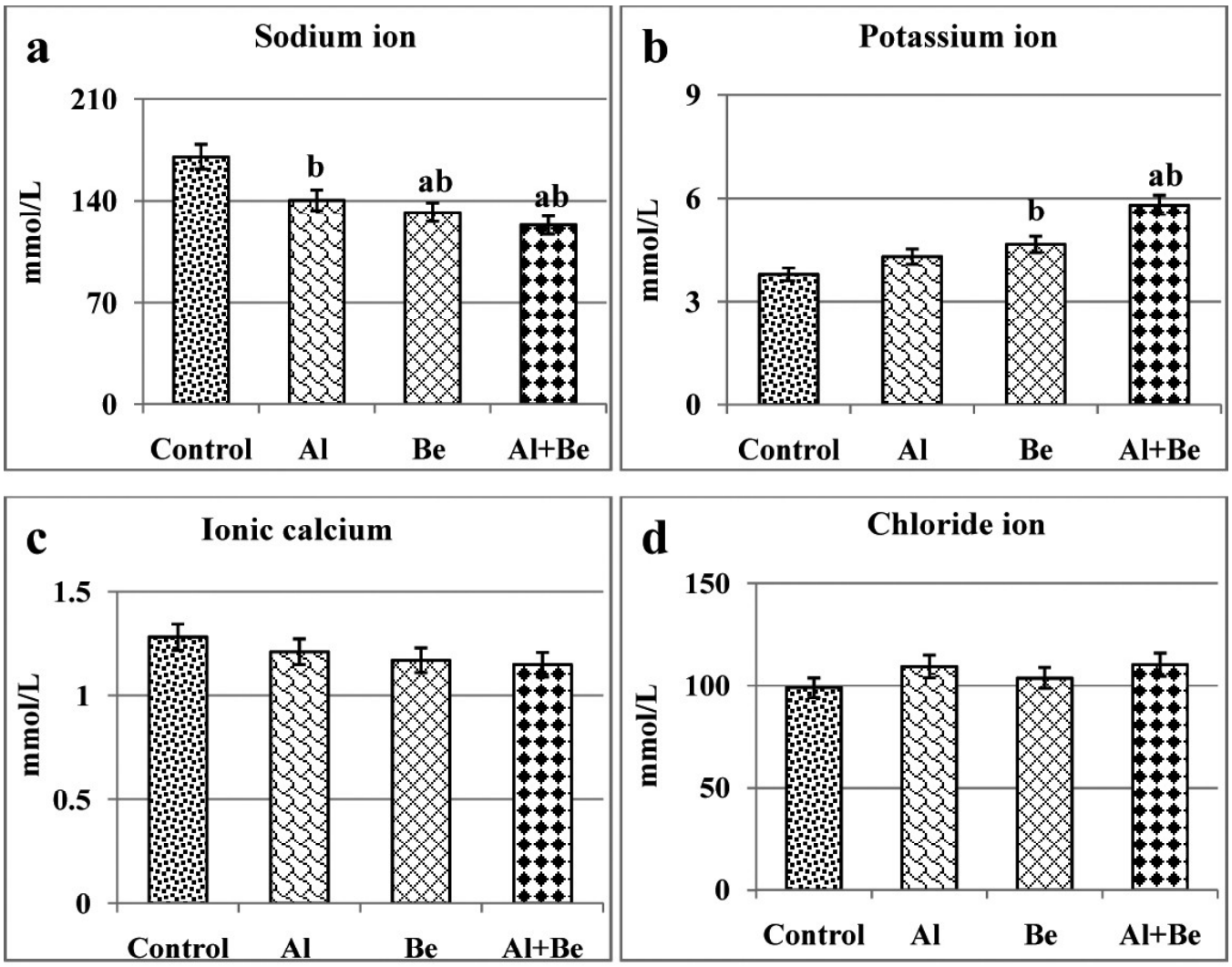
Parameters	PLT	PLCR	PLSR	MPV	WBCs	PCT
F variance	19.464[@]	1.415	19.464[@]	3.470[@]	7.745[@]	4.543[@]

Fig. 2 : Toxic effects of sub-chronic exposure to aluminum and beryllium on hematology and procalcitonin.

megakaryocyte function, resulting in decreased production and maturation of platelets[6,4]. Oxidative damage due to combination of Al and Be could induce fragmentation of large platelets that decreased MPV levels[15]. Decreased MPV level reflects an immune-mediated inflammatory response[27]. The combination of Al and Be could enhance oxidative stress[26,34], thus, excessive lipid peroxidation in RBCs and bone marrow remarkably increased oxidative stress, which stimulated bone marrow to produce more WBCs[10,23]. The Al and Be bind to proteins and are recognized as antigens, which further stimulates immune response. Increased platelet counts suggested an elevated rate of megakaryopoiesis and thrombopoietin activity. Under toxic conditions, large, immature, and hyperactive platelets are released from the bone marrow, indicating platelet activation during inflammatory responses, which collectively raised PLSR[3]. Bacterial infections, tissue damage and sepsis are typical conditions associated with elevated procalcitonin levels[11,25].

Serum electrolyte analysis

Electrolytes play a vital role in nerve signaling, muscular coordination, enzymatic activity, fluid, pH balance and cellular homeostasis[17]. Fig. 3 indicates toxic consequences on serum electrolytes after exposure to



Data are presented as mean ± SE (n=6); [a]Control vs Al, Be, Al+Be at P≤ 0.01; [b]Control vs Al, Be, Al+Be at P≤ 0.05; [@]significant for ANOVA				
Parameters	Na^+	K^-	Ca^{2+}	Cl^-
F variance	8.06[@]	10.08[@]	0.89	0.977

Fig. 3: Status of serum electrolytes after aluminum and beryllium induced toxicity

Al^{3+}, Be^{2+} and their combination. Exposure to Al alone significantly decreased Na^+ level in serum at $P \leq 0.05$, whereas Be and combination of Al and Be significantly decreased Na^+ level in serum both at $P \leq 0.01$ and $P \leq 0.05$ (fi. 3 a). Reduced Na^+ level in serum was due to disrupted cell membranes and interference of Al and Be in sodium-potassium pump, which allowed more Na^+ ions to leak into the cells, decreasing its level in the blood[9]. Significantly elevated K^+ level was observed after exposure to Be alone at $P \leq 0.05$, whereas combination of Al and Be both at $P \leq 0.01$ and $P \leq 0.05$) (fig. 3 b). Exposure to Al and Be could lead to metabolic acidosis, where the blood becomes highly acidic. In response to acidosis, K^+ ions shift from inside cells into the bloodstream, raising K^+ in serum[32]. No significant alteration was noticed Ca^{2+} and Cl^- level in serum (fig. 3 c-d).

Conclusion

Sub-chronic exposure to Al and Be and their combination induced significant alterations in some of the hematological parameters and serum electrolyte levels that reflected early sign of systematic toxicity. Thus, exposure to combination of Al and Be exerted more toxic effects as compared to their individual exposure even at low doses.

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