ZANCO Journal of Pure and Applied Sciences

The official scientific journal of Salahaddin University-Erbil
ZJPAS (2016), 28 (5); 19-32

Effects of Potassium and Magnesium on Some Hematological Profiles in Two Kidney, One Clip- Hypertensive and Normotensive Rats

Hawzeen K. Othman, Ismail M. Maulood and Almas M. R. Mahmud

Department of Biology, College of Science, University of Salahaddin -Erbil, Erbil, Kurdistan Region, Iraq

A R T I C L E I N F O

Article History:
Received: 29/05/2016
Accepted: 17/07/2016
Published: 28/11/2016

Keywords:
Haematological parameters,
2K1C hypertension,
Potassium ion,
Magnesium ion

***Corresponding Author:**
Hawzeen K. Othman
hawaphysio@yahoo.com

A B S T R A C T

In the current study the effects potassium and magnesium ions administration on blood parameters in 2-kidney one clip (2K1C) hypertensive and normotensive rats were investigated. Seventy male albino rats were separated into two experiments. The first experiment was performed to test the effects of potassium and magnesium on some haematological parameters included blood cell count, and platelet (PLT) indices in 2K1C hypertensive rats. The second experiment was done on the normotensive rats measuring the same parameters in the first experiment. The high blood pressure of 2K1C resulted in a significant elevation in RBCs, hemoglobin (HGB), WBCs count, granulocytes, monocytes and PLT count, while; statistical analysis showed a significant decrease in mean platelet volume (MPV) in 2K1C group. Moreover, non-significant changes were observed in other blood parameters in 2K1C hypertensive rats. Supplementation of potassium decreased RBCs count, hematocrit (HCT), WBCs count, granulocytes, monocytes and PLT count. While it had non-significant effect in HGB, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), lymphocytes, MPV and PDW. Magnesium alone and in combination with potassium caused not significant changes in RBCs, HGB, MCV, MCH, lymphocytes, MPV and MDW, while, significant decreases were recorded in granulocytes, monocytes and PLT in comparison to 2K1C rats. In the second experiment, potassium alone and in combination with magnesium caused no significant differences in RBCs, HGB, HCT, MCV and MCH, wearers, RBCs, HGB and HCT were elevated by magnesium supplementation. On the other hand, anon-significant changes were noticed MCV and MCH level in magnesium treated rat group. Also, non-significant differences were recorded among the experimental groups in WBCs, granulocytes, lymphocytes, and monocytes, PLT, MPV and PDW. Using magnesium and potassium ions supplementation alone or their combinations could improve the elevated WBCs, RBCs and PLTs counts in 2K1C hypertensive rats.

1. INTRODUCTION

The 2-kidney one clip rats were previously studied appropriately as a renin–angiotensin system (RAS) dependent model of hypertension (Cervenka *et al.,* 2001), in which hemodynamically significant narrowing of one renal artery chronically reduces renal perfusion and increases RAS activities (Martinez-Maldonaldo, 1991). The increased aldosterone and vasopressin synthesis and overstimulation of the sympathetic nervous system have also contributed to induce high blood pressure in 2K1C hypertension (Pawlk *et al.,* 2008). Both clinical and experimental studies demonstrated the association between activation of the RAS and increased erythropoiesis (Cole *et al.,* 2000). However, a number of studies clearly demonstrated that in addition to hypertension, renal artery constriction in 2K1C also causes hyper coagulation state (Pawlk *et al.,* 2008). As well as renal inflammation (Ruiz- Ortega *et al.,* 2001). In addition, Ang II increases production inflammation markers through nuclear factor-kappaB (NF-((kappa)B)-mediated induction of cytokine and reactive oxygen species (ROS) in 2K1C hypertension (Bivol *et al*., 2008).

Potassium ion is the most abundant cation in the intracellular fluid (Gyton and Hall, 2010). It is well documented that maintaining the proper distribution of potassium across the cell membrane is critical for normal cell functions (Bif, 2015). Potassium ions are known to stimulate the activities of some different important enzymes that participate in variety of metabolic processes (Jelenic, 1971). In addition, studies demonstrated that increasing potassium intake has been documented to decrease inflammatory cytokines (Rigsbye *et al*., 2008).

Magnesium ion has been named the forgotten cation, plays an important role in different cellular and metabolic reactions including, lipid and carbohydrate metabolism, nucleic acids and protein synthesis, ionic pumps, and calcium-channel function (Moslehi *et al.,* 2012). Studies suggested that magnesium ion intake was associated with lower risks of metabolic syndrome (Song *et al.,* 2007), oxidative stress (Moslehi *et al*., 2012), hypertension (Sonita and Touyz, 2007) and inflammation (King *et al.,* 2007).

Also, high magnesium concentration has been shown to increase hemoglobin levels in athletes (Cinar *et al*., 2007), improves anemia in mouse beta-thalassemia (De-franceschi *et al.,* 1997), alter erythrocytes membrane structure, decreases reticulocytosis, spherocytosis, microcytosis and erythroid hyperplasia of the bone marrow in rat erythrocytes (Jeng *et al.,* 1982). In the present study, we investigated the effects of dietary potassium and magnesium intake on blood parameters in 2K1C hypertensive and normotensive rats.

2. MATERIALS AND METHODS

2.1 Experimental design

Two experiments were carried out.

2.1.1. Experiment I

Forty-two rats were divided into six groups each seven rats and the treatments were continued for four weeks. The group one received standard rat chaw and tap water (Maulood, 2005) and represents control rats. The rats in the second group underwent sham-operated surgery and received standard rat chaw and tap water. The rats in 2K1C group underwent clipping procedure and received normal rat chaw and tap water. Other groups that underwent a clipping procedure and

received KCl(80g/kg b.w),MgSO4(80g/kg b.w) and their combination were called (2K1C+KCl),(2K1C+MgSO4) and (2K1C+KCl+MgSO4) groups, respectively.

2.1.2. Experiment II

Twenty-eight rats were divided into four groups each containing seven rats. Group one: act as a control group and received standard rat chow and tap water. Group two received KCl(80g/kg diet), while the third group received $MgSO_4$ (80g/kg diet) and the fourth group-received combination of KCl and $MgSO_4$ (160g/kg diet).

2.2. Induction of 2K1C Hypertension

The experimental rats were anesthetized and their left kidney exposed through a flank incision. After separating the renal artery and vein, a silver clip with an internal diameter of 0.25 mm was placed around the renal artery. The whole procedure on the sham group was done except clipped silver clip around left renal artery (Catter *et al*., 1990).

2.3. Collection of blood samples

The rats were anesthetized using a combination of ketamine hydrochloride (35 mg/kg) and xylazine (5mg/kg) (Liard *et al.*, 1996). Blood samples were taken by cardiac puncture into chilled tubes with EDTA (4.5 mM as an anticoagulant) and centrifuged at $+4C^o$ for 15 minutes; then plasma was stored at -80^oC (Sony, Ultra low, Japan).

2.4. Haematological analysis

Hematological parameters were measured by Coulter Counter (Celltac- MEL-6400k, Nihon kohen Corporation, Tokyo, Japan).

2.5. Statistical analysis

All data were expressed as means ± standard error (SE) and statistical analysis was carried out using available statistical software (Statistical package for social science social (SPSS) version 24). Data analysis was made using one-way analysis of variance (ANOVA). The comparisons among groups were done using Duncan post hoc analysis. P values <0.05 were considered as significant.

3. RESULTS

3.1. Effects of potassium and magnesium on hematological parameters in 2K1C hypertensive rats

Statistical analysis shows that RBC counts and hematocrite level significantly ($p<0.05$) increased in the 2K1C hypertensive rats compared with control and sham groups, while administration of KCl alone in 2K1C hypertensive rats caused a significant decrease in RBC counts and HCT when compared with 2K1C hypertensive rats. Weareas, combination of KCl and MgSO4 showed a non-significant change in RBC counts and significant decrease of HCT level compared with 2K1C hypertensive rats. Hypertensive rats along with $MgSO_4$ did not change RBCs and HCT compared with 2K1C hypertensive rats (Table 1 and Figure 1, A and C).The present results revealed that there were no significant differences ($P<0.05$) in HGB levels among the experimental groups (Table1 and Figure1, B). Neither 2K1C nor KCl and MgSO4 administration changed the MCV and MCH values significantly in compared to the control group.

Renal artery constriction in 2K1C hypertensive rats caused significant (P<0.05) elevation in WBCs, Granulocytes and monocytes. While, they decreased significantly in 2K1C hypertensive rats supplied with KCl, $MgSO_4$ and their combination when compared with 2K1C hypertensive rats (Table 2). No significant difference was observed in lymphocytes value among the experimental groups (Table 2).

The PLT was increased significantly (P<0.05) in 2K1C hypertensive rat group compared with control and sham groups while, a significant (P<0.05) reduction occurred in PLT count in 2K1C hypertensive rats supplied with KCl, $MgSO_4$ and their combination compared with 2K1C hypertensive rats (Table 3 and Figure 2, A). On the other hand, statistical analysis revealed significant decrease in MPV in 2K1C hypertensive rats when compared with control and sham groups. However, KCl, $MgSO_4$ and their combination treated rat groups showed non-significant changes in MPV when compared to 2K1C hypertensive rats. (Table 3 and Figure 2, B). PDW was not changed significantly between the control group and the 2K1C group. On the other hand, KCl, MgSO4 and their combination did not change it significantly (Table 3 and Figure 2, C).

3.2. Effects of potassium and magnesium on hematological parameters in normotensive rats

Red blood cell counts and HGB level showed no significant changes (6.42±0.1)(12.02±0.1), (6.64±.1) (11.52±0.3) in KCl and combination of (KCl and $MgSO_4$) treated rats, while, it increased significantly (*P*<0.05) in animals provided with diet supplemented with $MgSO_4$ (7.70±0.1), (13.82±0.2) when compared with control (6.33±0.3), (12.47 ±0.5) rat groups.(Figure3, A and B).Hematocrit level was increased significantly (P<0.05) in $MgSO_4$ treated rats (46.96±0.9) in comparison with the control (42.32±2.1) group. Whereas HCT didn't change significantly in KCl and combination (KCl and MgSO4) treated rat groups (40.90±0.97) and (40.00±1.4), respectively, compared with the control animals (Figure3, C).

MCH level in KCl treated rats showed no significant difference (60.78 ±0.8) versus control group. While, a significant (p<0.05) decrease was occurred in MCH of rats treated with $MgSO_4$ and combination of ($MgSO_4$ and KCl) (17.41±0.21) and (17.82±0.18), respectively, in comparison with control (19.12 ± 0.5) rats (Figure 4,A). Statistical analysis revealed that there were no significant differences (*P*<0.05) between MCV values of control, KCl, and combination of KCl+ $MgSO_4$ treated groups, when compared with control group (Figure 4, B). During the four weeks of the study-period, there were no significant differences among the experimental groups in WBC, granulocytes, lymphocytes and monocytes (Table 4). KCl and MgSO4 treatments didn't cause significant differences in platelets and platelet activation marker (MPV and PDW) when compared with the control rats (Table5).

Table 1: Effects of potassium and magnesium on RBC, HG, HCT, MCV and MHC in 2K1C hypertensive rats

Groups	RBCs	HGB	HCT	MCV	MCH
	($X10^6/\mu m\ 3$)	g/dL	%	fl	pg
Control	6.72±0.31[a]	12.94±0.64[a]	45.70±1.[bc]	58.77±1.5 [a]	19.12 ± 0.5[a]
Sham	6.63±0.11[a]	13.88±0.37 [a]	42.87±0.6[ab]	59.15 ±1.[a]	19.06±0.53 [a]
2K1C	8.05±0.39 [b]	14.2±0.29 [a]	48.52±1[c]	61.53±1.8 [a]	18.86±0.58 [a]
2K1C+KCl (80g/kg diet)	6.42± 0.29 [a]	13.61±0.97 [a]	40.11±1 [a]	62.80 ±1.6 [a]	18.86±0.58 [a]
2K1C+$MgSO_4$ (80g/kg diet)	7.12±0.8 [ab]	12.48±0.38 [a]	45.65±0.8[bc]	63.1±0.6 [a]	17.54±0.27 [a]
2K1C+KCl+ $MgSO_4$ (160g/kg diet)	7.3± 0.35 [ab]	12.47±0.29[a]	45.65±0.8[bc]	66.78 ±0.9 [a]	17.70 ± 0.3 [a]

2-kidney one clip (2K1C), red blood cells (RBC), hemoglobin (HGB), hematocrite (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)

Data presented as mean ± S.E The same letters mean non significant differences while the different letters mean significant differences at $p<0.05$.

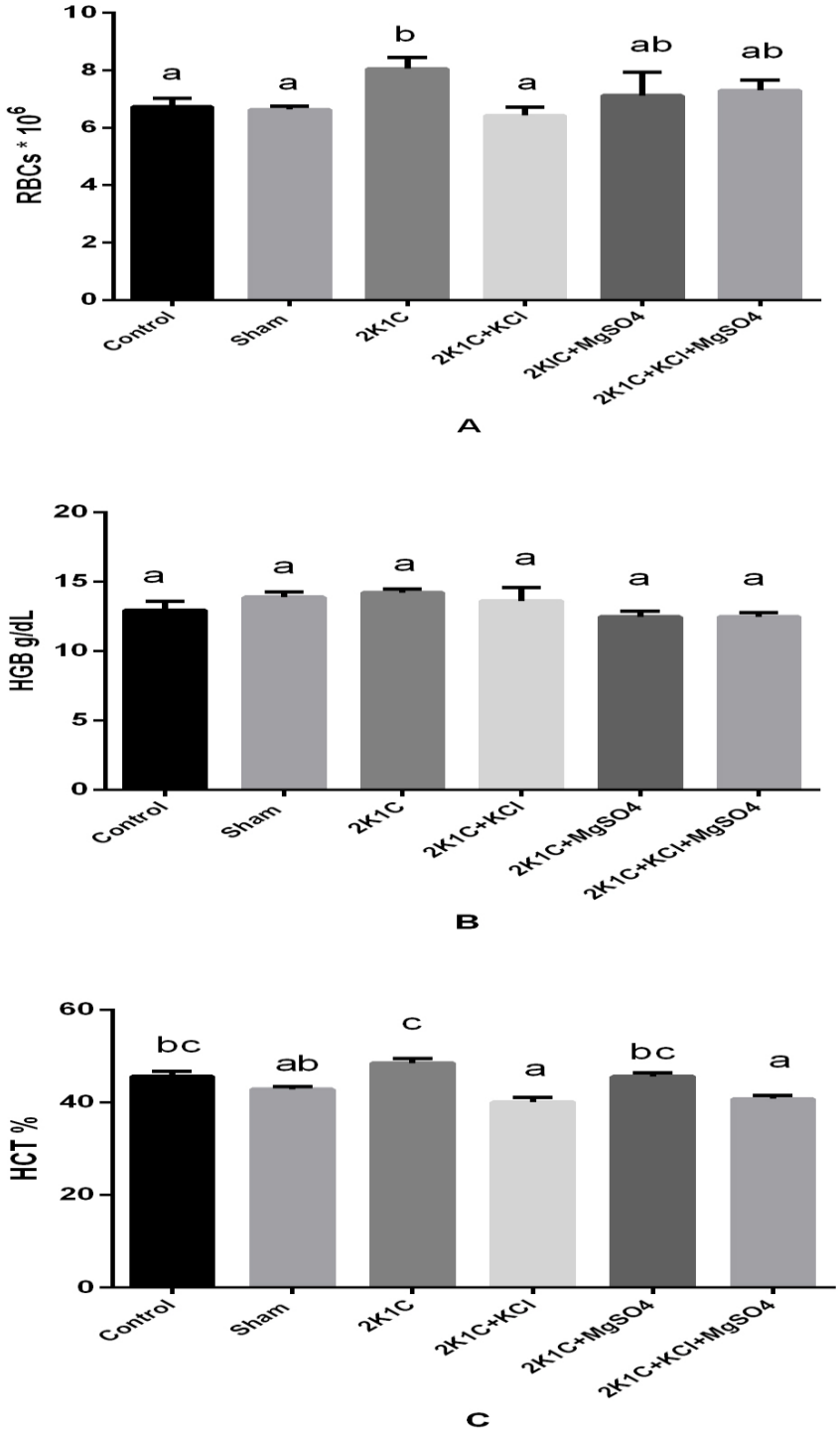

Figure (1): Effects of potassium, magnesium and their combination on (A) RBCs (B) HGB and (C) HCT in 2K1C hypertensive rats. The 2K1Chypertensive rats were compared with control and sham groups while (2K1C+ KCl), (2K1C+ MgSO4) and (2K1C+KCl+MgSO4) groups were compared with 2K1Chypertensive rats.

Table 2: Effects of potassium and magnesium on WBCs count, Granulocytes, Lymphocytes and Monocytes in 2K1C hypertensive rats

Groups	WBCs ($X10^3/\mu m\ 3$)	Granulocytes %	Lymphocytes %	Monocytes %
Control	6.11±0.3^{ab}	15.76 ±1^{a}	63.50±0.8^{a}	6.68± 0.6 ^{a}
Sham	8.1 ± 0.7^{b}	12.26±0.8 ^{a}	63.72±0.2^{a}	7.76±0.4^{a}
2K1C	13.05± 1 ^{c}	24.03±1 ^{b}	66.84.±0.8^{a}	10.65±0.6^{b}
2K1C+KCl (80g/kg diet)	7.66± 0.8^{ab}	13.20±0.8 ^{a}	67.66±0.5^{a}	6.62 ±0.5 ^{a}
2K1C+$MgSO_4$ (80g/kg diet)	6.1±0.3^{ab}	13.80 ± 1 ^{a}	71.02±0.4^{a}	7.76±0.9^{a}
2K1C+KCl+ $MgSO_4$ (160g/kg diet)	5.46± 0.7 ^{a}	17.33± 1^{a}7	1.98±0.8 ^{a}	7.76±0.9^{a}

2-kidney one clip (2K1C), White blood cells (WBC)
Data presented as mean ± S.E
The same letters mean non significant differences while the different letters mean significant differences at $p<0.05$.

Table 3: Effects of potassium and magnesium on PLT, MPV and PDW in 2K1C hypertensive rats

Groups	PLT(x103/µl)	MPV (fl)	PDW(%)
Control	440.14 ± 55.1 ^{ab}	4.65 ± 0.19 ^{c}	13.14 ± 0.20 ^{a}
Sham	369.00 ± 32.05 ^{a}	4.46 ± 0.16 ^{c}	13.18± 0.25 ^{a}
2K1C	656.60 ± 81.6 ^{d}	3.56 ± 0.13 ^{ab}	13.21 ± 0.26 ^{a}
2K1C+KCl (80g/kg diet)	489.00 ± 79.5 ^{bc}	3.87 ± 0.14 ^{b}	13.46 ± 0.24 ^{a}
2K1C+$MgSO_4$ (80g/kg diet)	534.80 ± 28.4 ^{c}	3.64 ± 0.22 ^{ab}	13.46 ± 0.11 ^{a}
2K1C+KCl+ $MgSO_4$ (160g/kg diet)	571.60 ± 81.6 ^{c}	3.14± 0.09 ^{a}	13.60. ± 0.22

2-kidney one clip (2K1C), platelete (PLT), mean platelet volume (MPV), platelet distribution width (PDW)
Data presented as mean ± S.E
The same letters mean non significant differences while the different letters mean significant differences at $p<0.05$.

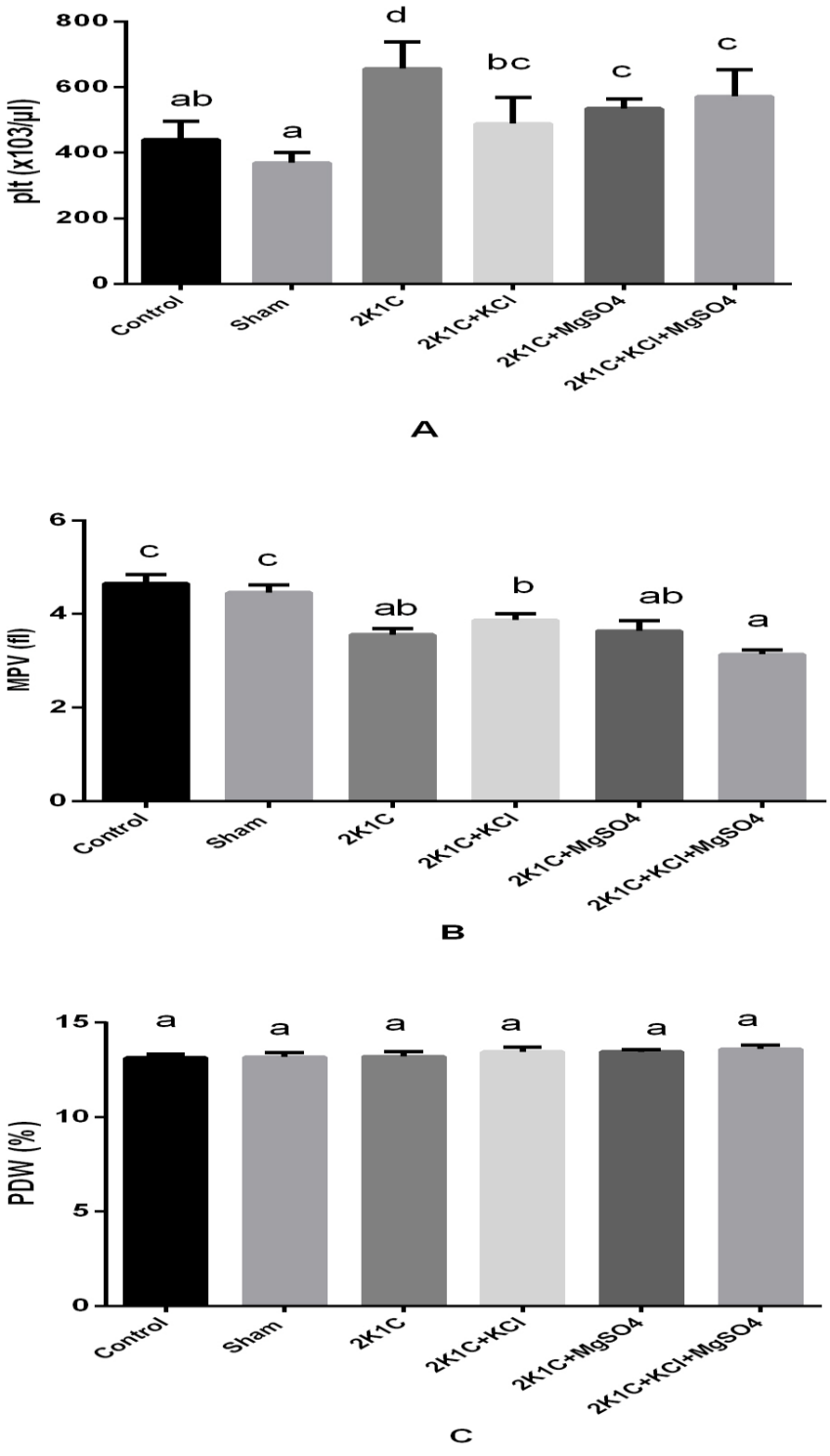

Figure (2): Effects of potassium, magnesium and their combination on (A) PLT (B) MPV and (C) PDW in 2K1C hypertensive rats. The 2K1Chypertensive rats were compared with control and sham groups while (2K1C+ KCl), (2K1C+ MgSO4) and (2K1C+KCl+MgSO4) groups were compared with 2K1Chypertensive rats.

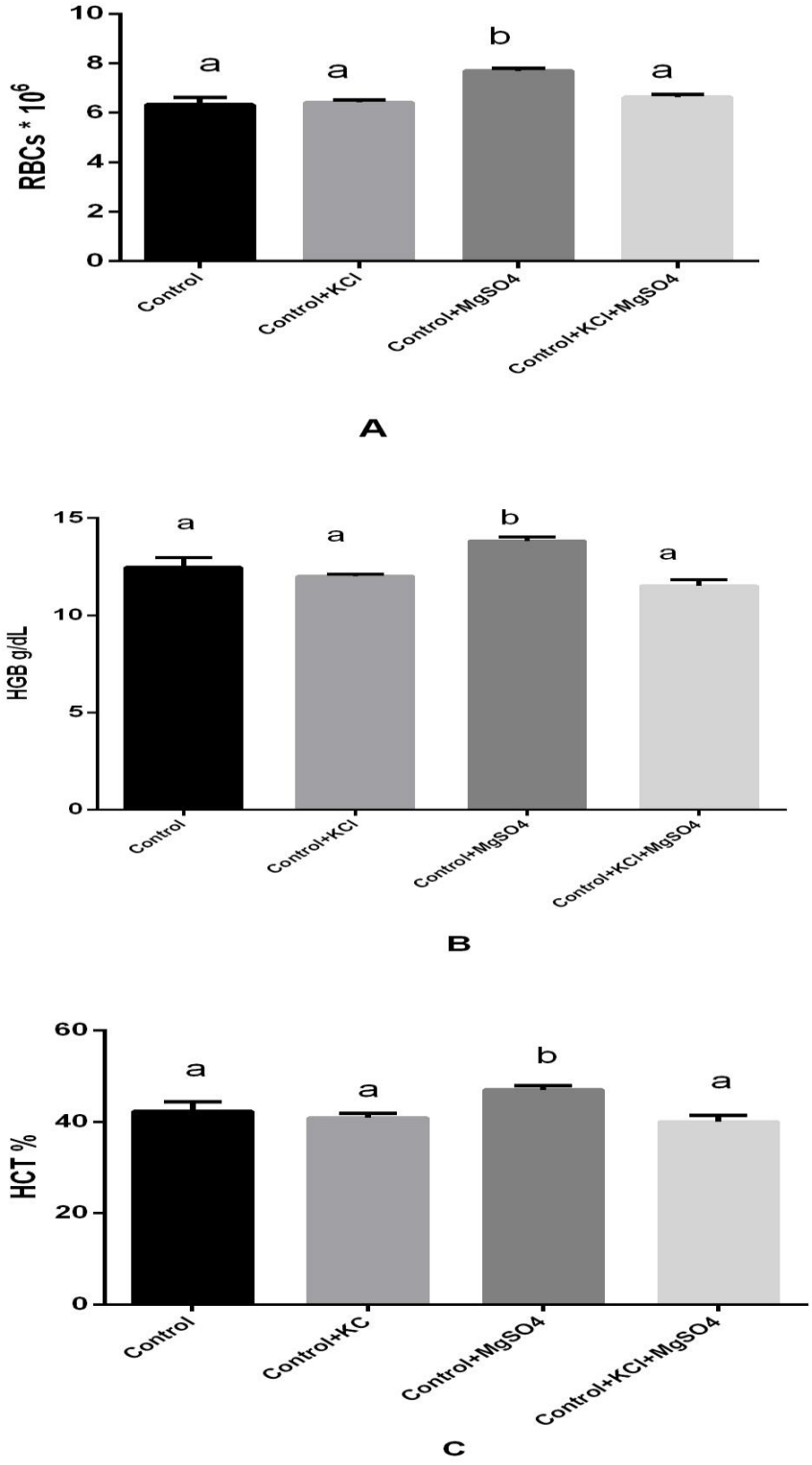

Figure (3): Effects of potassium, magnesium and their combination on (A) RBC (B) HGB and (C) HCT in normotensive rats. The (Control+ KCl), (Control + MgSO4) and (Control+KCl+MgSO4) groups were compared with control group.

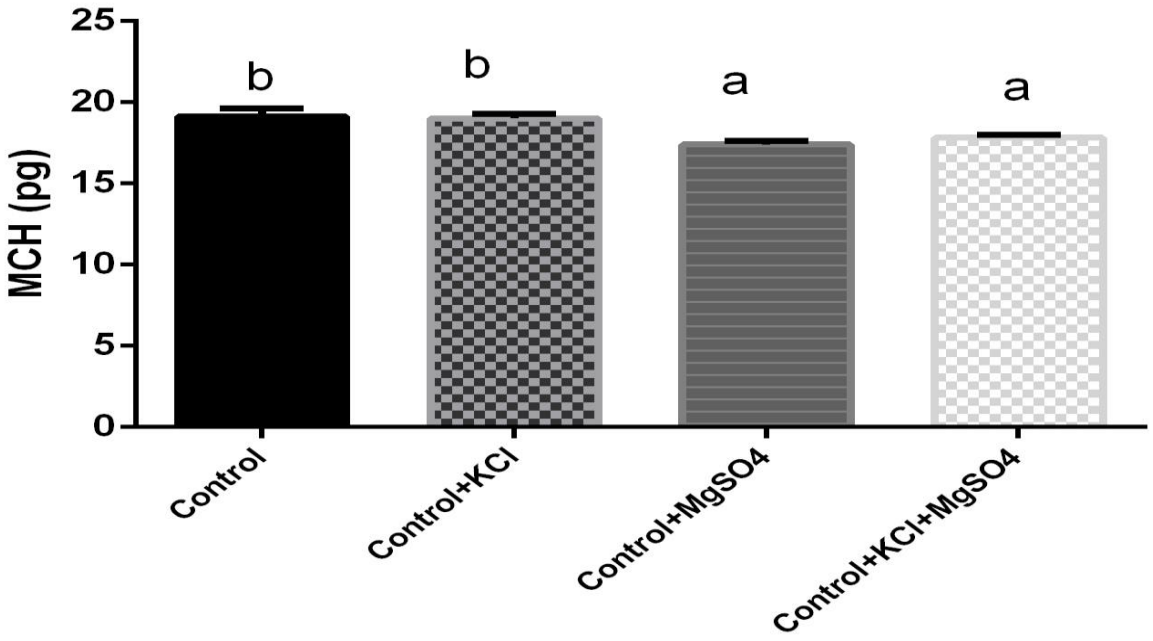

Figure (4): Effects of potassium, magnesium and their combination on RBC indices (A) MCH in normotensive rats. The (Control+ KCl), (Control + MgSO4) and (Control+KCl+MgSO4) groups were compared with control group.

Table 4: Effects of potassium and magnesium on WBC, Granulocytes, Lymphocytes and Monocytes in normotensive rats

Groups	WBCs	Granulocytes	Lymphocytes	Monocytes
	$X10^3$ /μm 3	%	%	%
Control	6.35 ± 0.4[a]	22.26 ± 2.5 [a]	59.96 ± 2.2 [a]	5.36 ± 0.5 [a]
Control+KC (80g/kgb.w)	6.45 ± 0.9[a]	26.68 ± 2.5 [a]	67.86 ± 1.2 [a]	5.94± 0.4[a]
control+ $MgSO_4$ (80g/kgb.w)	6.82 ± 1.1[a]	29.22 ± 4.2 [a]	57.70 ± 4.3 [a]	6.10 0.3[a]
Control+ KCl+ $MgSO_4$(80g/kgb.w)	8.37 ± 0.5[a]	29.9 ± 2 [a]	57.02 ± 1.9 [a]	6.43 ± 0.2 [a]

White blood cells (WBC)
Data presented as mean ± S.E
The same letters mean non significant differences while the different letters mean significant differences at $p<0.05$.

Table 5: Effects of potassium and magnesium on PLT, MPV and PDW in normotensive rats.

Groups	PLT(x103/µl)	MPV (fl)	PDW(%)
Control	414.00 ± 11.0[a]	3.74 ± 0.8 [a]	15.02 ± 0.20 [a]
Control+KC (80g/kgb.w)	447.50 ± 15.5[a]	3.81 ± 0.1 [a]	15.27± 0.3 [a]
control+ $MgSO_4$ (80g/kgb.w)	472.00 ± 20.1[a]	3.97 ± 0.1 [a]	14.84 ± 0.4 [a]
Control+ KCl+ $MgSO_4$ 80g/kgb.w	478.66 ± 18.6[a]	3.97 ± 0.6 [a]	14.91 ± 0.2 [a]

2-kidney one clip (2K1C), platelete (PLT), mean platelet volume (MPV), platelet distribution width (PDW)
Data presented as mean ± S.E
The same letters mean non significant differences while the different letters mean significant differences at $p<0.05$

4. Discussion

The results show that experimentally induced-hypertension in 2K1C rats produced a significant increase in RBCs count and HCT level. The mechanisms responsible for this increase in RBC count and HCT level are still largely unknown, but it is well documented that Ang II produced by renal artery constriction and plays a critical role in erythropoiesis (Valhakos *et al*., 2010). However, in a study it was shown that Ang II stimulates proliferation of erythroid progenitor cells via Ang II receptor, type 1*in vitro* (Macdougall, 1999). AngII, infact, has an a stimulator effect of erythropoietin production (Jelkmann, 2011) and it could increase erythropoiesis (Haen, 1995). Moreover, the stimulatory effect of Ang II on erythropoiesis may associate with its stimulatory effect on the adrenal cortical cells to secrete androgens (Valahakos *et al*., 2003).

In the present study, the dietary supplementation of KCl through unknown mechanism significantly lowered RBCs in hypertensive rats. This is in agreement with that reported by (Hassan *et al*., 2011) who found that potassium chloride supplementation increased some hematological parameters of golden montazah hens under hot climate condition. The main reason for this result might be due to the ability of potassium ion to suppress rennin and AngII secretion (Suzuki *et al*., 1981), that have been reported to stimulate the proliferation of the progenitor cells of erythrocytes (Rodgers *et al.*, 2000). It has also been reported that potassium enhances nitric oxide (NO) production (Adrougue and Madias, 2007), which in turn inhibits growth, differentiation, and hemoglobinization of primary erythroid cells (Han *et al*., 2002).

Our results show that magnesium supplementation for a period of four weeks results in increase in the number of RBCs and hemoglobin level in normotensive rats. Although a correlation between magnesium and increase RBC has been reported in a variety of clinical and pathological studies, the exact mechanism of this association has not been fully understood (Oinar *et al*., 1993). Magnesium's ability to act as a cofactor for more than 300 enzymes could provide an explanation for the increase RBCs count, since it might be possible that erythropoiesis would be induced by the increase of magnesium intake (Swaminathan, 2003). However, magnesium has been shown to improve red blood cell hydration through reduction of K-Cl co-transport activity and it also decreases the number of dense sickle erythrocytes (Oiner, 1993). On the other hand, the reduction in both reticulocyte numbers and percentage of immature reticulocytes induced by magnesium intake (Lueia de *et al*., 1997) might be another possible mechanism for increasing RBCs in our results. Also, magnesium has been reported to potentiate the maintenance of RBCs glutathione concentration (Jeng *et al*., 1982), which protects haemoglobin protein from denaturation under oxidative stress (Namakkal *et al.*, 2004).

The number of WBC was increased in 2K1C hypertensive rats. It is well established that an increase the WBC count is an indicator of inflammation (Tzy-Haw *et al*., 2013) however our results confirm those of (Chang and Wei, 2015) as they concluded that, Ang II enhances leukocytosis through increases markers of inflammation. Angiotensin II may cause leucocytosis via it is ability to induce ischemia induced renal injury. However, the ischemic or necrotic area

in kidney secrets tumor necrosis factor-alpha cytokine (Maha *et al*., 2012), which enhances with granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) (William *et al*., 1993). The production of (G-CSF and GM-CSF) by Ang II could explain why neutrophil and total WBC counts were increased. Angiotensin II may also increases WBC through increase another inflammation markers such asinterlukin-6 and interleukin 1 beta (IL)-1β, nuclear tumor necrosis factor-kappa B (Carmine and Ernesto, 2006) and enhancing free radical generation (Alvarez and Sanz, 2001).

The present results show that potassium and magnesium administration decreased WBC value in both hypertensive and normotensive rats. (Rigsby *et al*., 2008) have shown that dietary potassium supplementation in stroke prone spontaneously hypertensive rats cause a dramatic reduction in the plasma concentration of pro-inflammatory cytokine, (IL-1β). Potassium has also been reported to decrease free radical formation (Kido *et al*., 2007) that may contribute to potassium's anti-inflammatory effects. On the other hand, (Moslehi *et al*., 2012) concluded from a study that magnesium deficiency stimulated both acute and chronic phase of inflammation. Increased intracellular calcium ions due to magnesium deficiency (Sonita and Touyz, 2007) and magnesium's ability to decrease C-reactive protein levels (King *et al*., 2007) could be the possible mechanisms by which magnesium decreases inflammation. Presumably, the inverse association between magnesium, potassium intake and WBCs count may be through their anti-inflammatory effects.

The obtained results confirmed that the renal artery constriction in 2K1C rat have stimulatory effect on thrombopoiesis because it produced a significant elevation in platelet counts. Our results were correlated with (Pawlk *et al.,* 2008) who reported that renal artery stenosis in 2K1C rats caused changes in megakaryocyte-platelet system. However, Ang II has been reported to stimulate the proliferation of megakaryocytes precursor cells of platelets (Rodgers *et al*., 2000). On the other hand, Angll's ability to enhance leukocytes adhesion to endothelial cells accompanied by accelerate fibrin formation and increase plasma level of endothelial plasminogen activator inhibitorhave been documented by (Mogielnicki *et al*., 2005).

The results of the current study showed a significant decrease in MPV in both experiments. In our finding, the decrease in MPV was associated with the increase in platelet count. It has been shown that the volume of platelet is negatively correlated with the number of it (Yardan *et al*., 2016).

Results of our study indicate that potassium and magnesium ions significantly decreased PLT count in hypertensive rats. The antithrombotic effects of potassium probably through enhancing NO production. However, (Schattner *et al.,* 2001) established that exogenous and endogenous NO sources are capable of inducing the apoptosis of megakaryocytic cell lines. It is well known that elevation in cytosolic calcium ion concentration is essential for platelet activation (Vara-Szabo *et al*., 2009).

In conclusion, the results suggested that using magnesium and potassium ions supplementation alone or their combinations could improve the elevated WBCs, RBCs and PLTs counts in 2K1C hypertensive rats.

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