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Research Article

The Effects of Human Recombinant Erythropoietin on Various Hemato-biochemical Parameters in Nephrectomized Rabbits

Muhammad Asif[1], Hamid Akbar[1], Waqas Haroon[2], Sana Saeed[2], Samia Mushtaq[3], Muhammad Ali[4], Asma Fatima[1], Muhammad Zahir[1], Abdul Aziz[5], Fazal Ur Rehman[1]

[1]*Department of Veterinary Surgery, University of Veterinary and Animal Sciences, Lahore, Pakistan.*
[2]*Department of Anatomy & Histology, University of Veterinary and Animal Sciences, Lahore, Pakistan.*
[3]*Department of Veterinary Sciences, Azad Jammu and Kashmir, University of Bhimber, Pakistan.*
[4]*Department of Pathobiology, University of Layyah, Layyah, Pakistan.*
[5]*Department of Veterinary Clinical Sciences, University of Poonch, Rawalakot, Pakistan.*

ABSTRACT

This study was aimed to evaluate the effects of exogenous human recombinant erythropoietin (rHuEPO) on various hemato-biochemical parameters before and after unilateral nephrectomy. A total of 12 adult healthy rabbits were selected and divided into two groups: experimental group A and control group B. The group A (n=6) were treated with rHuEPO @ 1000 IU via subcutaneous route and placebo group B (n=6) without rHuEPO treatment followed by unilateral nephrectomy. Blood sampling was performed three times; 1st five days before surgery, 2nd; just before surgery and 3rd was performed after 5th day of unilateral nephrectomy. Evaluation of hematological and biochemical parameters including red blood cells (RBCs), mean corpuscular volumn (MCV) hemoglobin (Hb),total leukocyte count (TLC), packed cell volume (PCV), reticulocyte count (RC) and platelets counts, serum creatinine and blood urea nitrogen (BUN) was done. The data was analyzed statistically by *t*-test using SPSS version 20. In group A, values of RBCs, MCV, Hb, PCV, RC and platelets count was high after nephrectomy as compared to group B with a significant difference ($p \leq 0.05$). Preoperative values of serum creatinine and BUN in group A was declined after 1st injection of rHuEPO at day 5th postoperatively. At day 10th there was rise in its value but this rise was non-significant ($p \geq 0.05$). It is concluded that, rHuEPO increases the process of erthythropoisis. Due to its safety, efficacy and lack of systemic effects, rHuEPO can be used as alternate therapy of blood transfusions and hemato-biochemical disorders while performing nephrectomy or any other surgical interventions.

Keywords: Human Recombinant Erythropoietin, Hematobiochemical, Rabbits, Nephrectomy.

Correspondence
Muhammad Asif
dr.asif078@gmail.com

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INTRODUCTION

Erythropoietin is a hormonal factor produced by peritubular cells of the kidney. Primarily, kidney is responsible for the regulation of erythropoiesis (Adamson et al. 1968). Erythropoietin (EPO) is an endogenous cytokine with anti-inflammatory, antiapoptotic, andneurotrophic properties (Eid et al., 2002). RHuEPO is used as an autologous blood donation clinically and available as a drug. It is used to treat renal or other types of anemia in rabbits which are associated with various diseases (Inoueet al. 1995). Their major function is the production of erythropoietin for RBCs synthesis, transport of water and salts, excretion of waste products from body,

regulation of acid base mechanism, detoxification of drugs, lipid metabolism and maintenance of blood pressure. There are different anomalies such as renal tumors, cysts, calcification of kidney, fatty infiltration of kidney, congenital defects and renal nephroliths that causes life threatening conditions like abnormal blood pressure, unbalanced carbohydrate mechanism, hypercholesterolemia and unequal fat distribution in the body (Zhao et al. 2008). These types of cases are subjected to complete or partial nephrectomy (Gieser and Fenves 2006).

Nephrectomy is a complex procedure because it may leads to bleeding, urinary tract infections, serious blood disorders, lethal change in blood parameters and even death. If kidney parenchyma is excised, it may lead to sharp decline in renal activity (Dong et al., 2017). Renal damage can lead to alteration in BUN and serum creatinine profile which are two major parameters to assess kidney function (Perera et al., 1995). While performing any surgical intervention, blood loss takes place during surgery that causes hypovolemia and lead to development of anemia. To minimize the effect of hypovolemia and anemia, surgeons go far blood transfusion or drug treatment like rHuEPO and iron. RBCs volume is restored by rHuEPO in patients undergoing autologous preoperative blood donation before doing surgical intervention (Gieser and Fenves 2006).

RHuEPO is a reasonable alternative therapy for anemic low-risk elective patients (hemoglobin ≤13 g/dL). Many days before surgery procedure, erythropoietin is given in conjunction with iron therapy. Recombinant human erythropoietin (rHuEPO) was developed in the mid-1980s and is commercially available in several forms (Evatt et al., 1976). RHuEPO helps to restore RBCs after blood loss during surgery (Gieser and Fenves 2006). Erythropoietin acts on undifferentiated stem cells which are already committed to become RBCs. Erythropoietin stimulates their proliferation and maturation into mature erythrocytes. Increased erythropoietin activity elevates the number of circulating RBCs and hemoglobin which ultimately increases oxygen carrying capacity of the blood and restores normal oxygen delivery to the tissues. Once normal oxygen delivery to the kidneys is achieved, decrease in erythropoietin production occurs until future requirements (Gieser and Fenves 2006).

To our knowledge, there are no studies that evaluated effects of injectable rHuEPOin nephrectomized rabbits. Therefore, current study is designed to investigate effects of exogenous rHuEPOon various hemato-biochemical parameters before and after unilateral nephrectomy.

MATERIALS AND METHODS

Experimental Design and Treatments

The study was conducted on 12 adult male healthy rabbits of any breed, sex and aged between 1 and 3 years, with body weights ranging from 2 kg to 3.5 kg. Rabbits (n=12) were divided into two groups: experimental group A (n=6) and control group B (n=6). Experimental group A was treated with rHuEPO (2000 I.U/kg body weight, Tropin®, Avior pharmaceutics®, Karachi, Pakistan). RHuEPO was injected at day 5th before surgical procedure and 2nd day after surgical procedure of unilateral nephrectomy (Flaharty et al. 1990). Control group B was treated without RHuEPO and underwent unilateral nephrectomy.

A thorough physical examination was done to find out any preoperative complications before surgery. All animals were inspected for ectoparasites and dipped with fipronil (Frontline Spray®, Boehringer Ingelheim, Germany). Three days before surgery, antibiotic enrofloxacin (Enroxsel®, 5-15mg/ kg body weight, twice a day, intramuscular, Selmore pharmaceutics®, Lahore, Pakistan) was administered to reduce probabilities of infection (Henke et al. 2005). During the complete experimental period, rabbits were placed at research cages in the Surgery Section, Department of Veterinary Surgery and Pet Sciences, UVAS, Lahore. Rabbits were not kept off feed as they don't vomit (Moore et al. 2015). The proposed surgical site was sterilized by using povidone-iodine (pyodine 7.5%, Brooks pharmaceutics®, Karachi, Pakistan).

This study and all the procedures were approved and conducted in accordance with rules and regulations of the Ethical Review Committee (Ethical Approval # DR/983) at the Department of Veterinary Surgery, University of Veterinary and Animal Sciences, Lahore, Pakistan**.**

Surgical Procedure

In each animal, surgical procedures were carried out via anesthetic agents ketamine (35 mg/kg, I.M, KNOX®, GlaxoSmithKline, Karachi, Pakistan) mixed with Xylazine Hydrochloride (5 mg/kg body weight, I.M, Xylacare®, Animalcare, Karachi, Pakistan) in a ratio of 2:1, respectively (Szabo et al., 2015) (Mapara et al. 2012). Atropine sulphate (0.2mg/kg, Atrovet®, Selmore pharmaceutics®, Lahore, Pakistan) was avoided as it degraded by the atropinase which already present in rabbits (Pablo et al. 1995) (Oslon et al., 1994).

A ventral midline laparotomy approach was used for surgery (Szabo et al., 2016) (Sabater et al., 2021). After locating

kidney in retro peritoneum, blood vessels including renal vein and renal artery were ligated with absorbable suture material. After that, complete kidney was removed surgically (Slatter 2005). After surgical intervention, abdomen was closed by standard closure technique by suturing the linea alba and sub-cutaneous tissues with synthetic absorbable suture (Vicryle®, Ethicone,Ohio, USA) and skin with non-absorbable suture material using slik no. 2/0 (PERMA HAND®, Ethicone, Ohio, USA). After surgery, the rabbits were kept in the recovery room to observe any post-operative complications. To minimize the chances of systemic infection, the antibiotic enrofloxacin (Enroxsel®, Selmore Pharma®) was given at 5–15 mg/kg intramuscular twice a day, to prevent from post operative complications (Hedley et al., 2018). Flunixin meglumine (1.1 mg/kg, I.M, loxin®, Selmore pharmaceutics®, Lahore, Pakistan) was administered @ for pain relief via intramuscular route (Mooket at. 2005). The rabbits were also administrated dextrose (30 ml /day, intravenous, Steri-fluid® 5%, Frontier dextrose Ltd, Lahore, Pakistan) 30ml per day twice a day, for 5 days. After 5 days, rabbits were subjected to liquid food, and after 10 days, they were gradually switched from semisolid food to a solid food.

Blood Sampling and Hemato-biochemical Parameters Evaluation

A blood sample of 2 ml was extracted from the jugular vein of each animal on days 0, 5, and 10, and transferred into a blood vacutainer containing anticoagulant (K2 EDTA) (Moore et al. 2015). Then blood samples were referred to the University Diagnostic Lab (ISO-certified/17025) UVAS Lahore. The hemato-biochemical parameters including RBCs, Hb, PCV, TLC, PLT, MCV, reticulocyte, BUN, and serum creatinine were evaluated at the University Diagnostic Lab, UVAS Lahore.

Statistical Analysis

The data was analyzed statistically by *t*-test using SPSS version 20. All results were indicated as mean ± SD; P≥0.05 showing no significant difference and P≤0.05 showing a significant difference (Daniel, 2010).

RESULTS

Hematological parameters including; red blood cells (RBC), Hemoglobin (Hb), packed cell volume (PCV), reticulocyte counts, blood urea nitrogen (BUN) and serum creatinine were evaluated. The red blood cells (RBC) showed that there was a significant difference between both groups in rabbits o day 5 and 10 (p=0.000). In Group A, the level of RBC (10^{12}/L) was 5.90 ± 07, 7.2 ± 0.37, and 7.6 ± 0.18 on day 0, day 5 and day 10, respectively. In Group B, the level of RBC (10^{12}/L) was 6.4 ± 0.89, 6.43 ± 0.92, and 4.96 ± 0.39 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of RBC in Group A and B is given in Figure 1.

The blood hemoglobin (Hb) showed that there was a significant difference between both groups in rabbits o day 5 and 10 (p=0.000). In Group A, the level of Hb (g/dl) was 11.92 ± 1.27, 14.16 ± 0.81, and 14.55±1.14 on day 0, day 5 and day 10, respectively. In Group B, the level of Hb (d/dl) was 12.36 ± 1.84, 12.50 ± 1.88, and 10.90 ± 1.60 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of Hb in Group A and B is given in Figure 2.

Table 1. Various Blood Parameters at Day 0, 5 and 10 of Group A and B in Rabbits.

Parameters	Group A (rHuEPO treated) (n=6) Mean ± S.D			Group B (without rHuEPO) (n=6) Mean ± S.D			P-Value
	Day 0	Day 5	Day 10	Day 0	Day 5	Day 10	
Red blood cells (10^{12}/L)	5.90±071	7.2±0.37	7.6±0.18	6.4±0.89	6.43±0.92	4.96±0.39	0.000
Hemoglobin (g/dl)	11.92±1.27	14.16±0.81	14.55±1.14	12.36±1.84	12.50±1.88	10.90±1.60	0.000
Packed cell volume (%)	34.21±0.63	48.36±3.23	50.83±1.33	35.58±2.42	38.03±2.67	31.78±1.29	0.000
Reticulocyte Count (%)	3.68±0.58	15.86±5.27	25.16±4.11	4.68±1.17	4.88±1.12	3.40±0.58	0.000
Blood Urea Nitrogen (mg/dl)	28.50±7.3	23.33±5.7	53.50±12.9	30.16±6.9	29±6.66	44±9.4	0.002
Serum Creatinine (mg/dl)	1.48±0.23	1.18±0.11	1.65±0.38	1.10±0.29	0.95±29	1.41±0.28	0.19

The blood packed cell volume (PCV) showed that there was a significant difference between both groups in rabbits o day 5 and 10 (p=0.000). In Group A, the level of PCV (%) was 34.21 ± 0.63, 48.36 ± 3.23, and 50.83 ± 1.33 on day 0, day 5 and day 10, respectively. In Group B, the level of PCV (%) was 35.58 ± 2.42, 38.03 ± 2.67, and 31.78 ± 1.29 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of PCV in Group A and B is given in Figure 3.

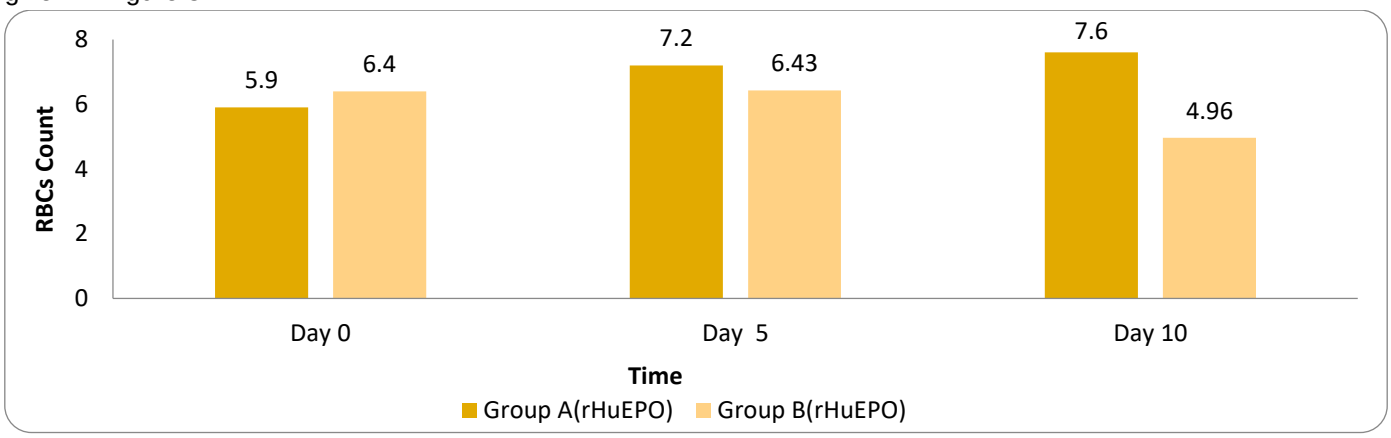

Figure 1. Mean Values of RBCs Between Group A and B.

The reticulocyte counts showed that there was a significant difference between both groups in rabbits o day 5 and 10 (p=0.000). In Group A, the level of reticulocyte counts (%) was 3.68 ± 0.58, 15.86 ± 5.27, and 25.16 ± 4.11 on day 0, day 5 and day 10, respectively. In Group B, the level of reticulocyte counts (%) was 4.68 ± 1.17, 4.88 ± 1.12, and 3.40 ± 0.58 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of reticulocyte counts in Group A and B is given in Figure 4.

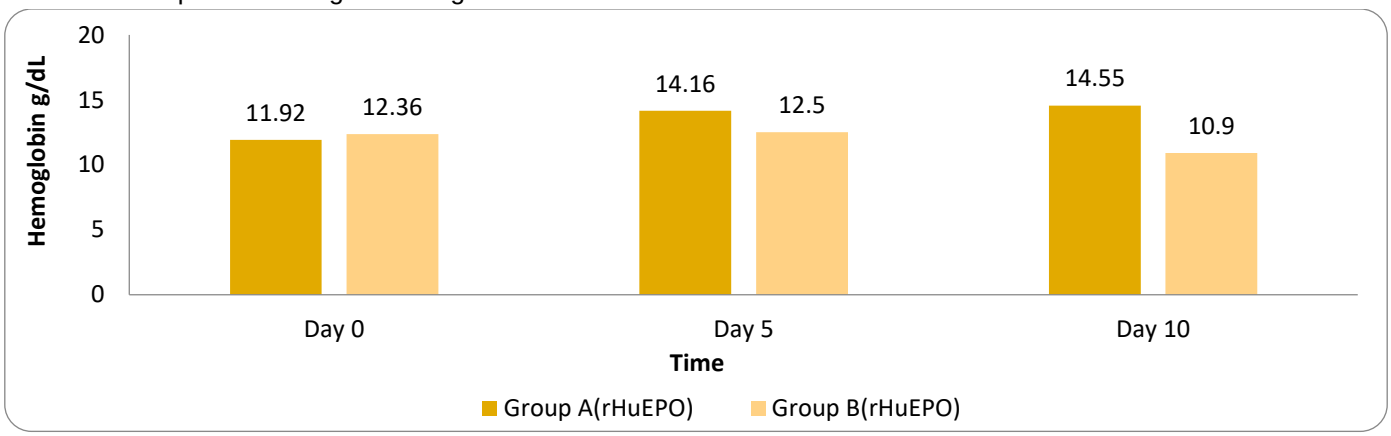

Figure 2. Mean Values of Hb of Group A and B.

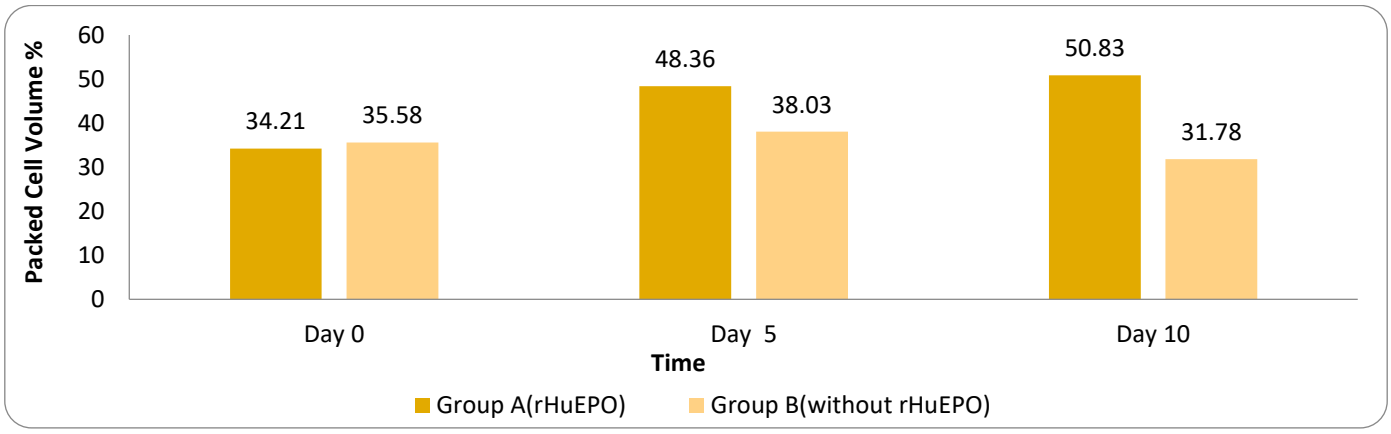

Figure 3. Mean Values of PCV of Group A and B.

The blood urea nitrogen (BUN) (mg/dl) showed that there was a significant difference between both groups in rabbits o day 5 and 10 (p=0.002). In Group A, the level of BUN (mg/dl) was 28.50 ± 7.3, 23.33 ± 5.7, and 53.50 ± 12.9 on day 0, day 5 and day 10, respectively. In Group B, the level of BUN (mg/dl) was 30.16 ± 6.9, 29 ± 6.66, and 44 ± 9.4 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of BUN in Group A and B is given in Figure 5.

The serum creatinine (mg/dl) showed that there was no significant difference between both groups in rabbits o day 5 and 10 (p=0.19). In Group A, the level of serum creatinine (mg/dl) was 1.48 ± 0.23, 1.18 ± 0.11, and 1.65 ± 0.38 on day 0, day 5 and day 10, respectively. In Group B, the level of serum creatinine (mg/dl) was 1.10 ± 0.29, 0.95 ± 29, and 1.41 ± 0.28 on day 0, day 5 and day 10, respectively. The graphical representation of mean values of serum creatinine in Group A and B is given in Figure 6.

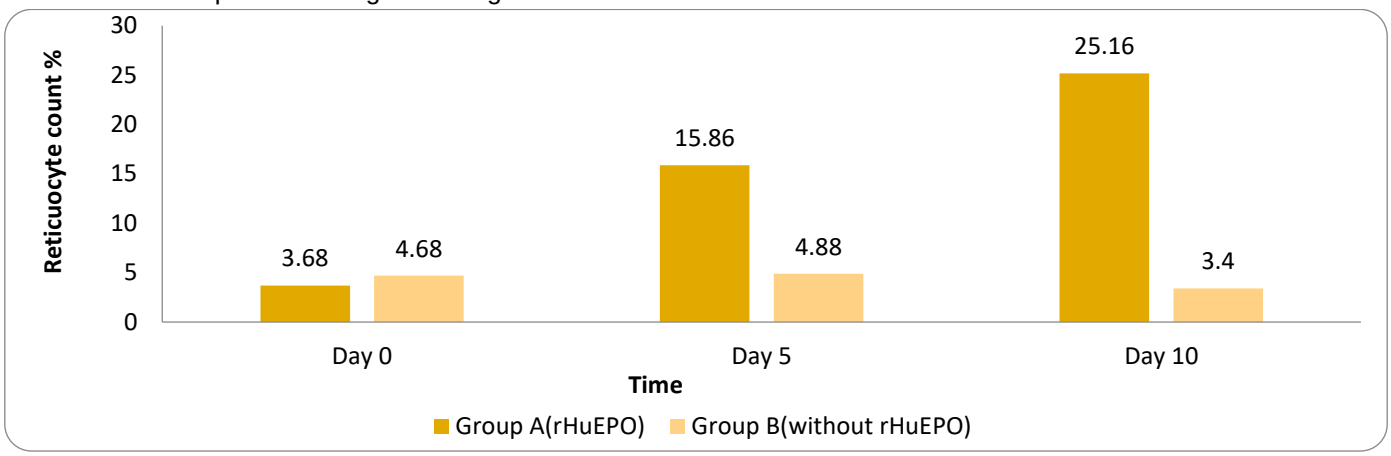

Figure 4. Mean Values of Reticulocytes of Group A and B.

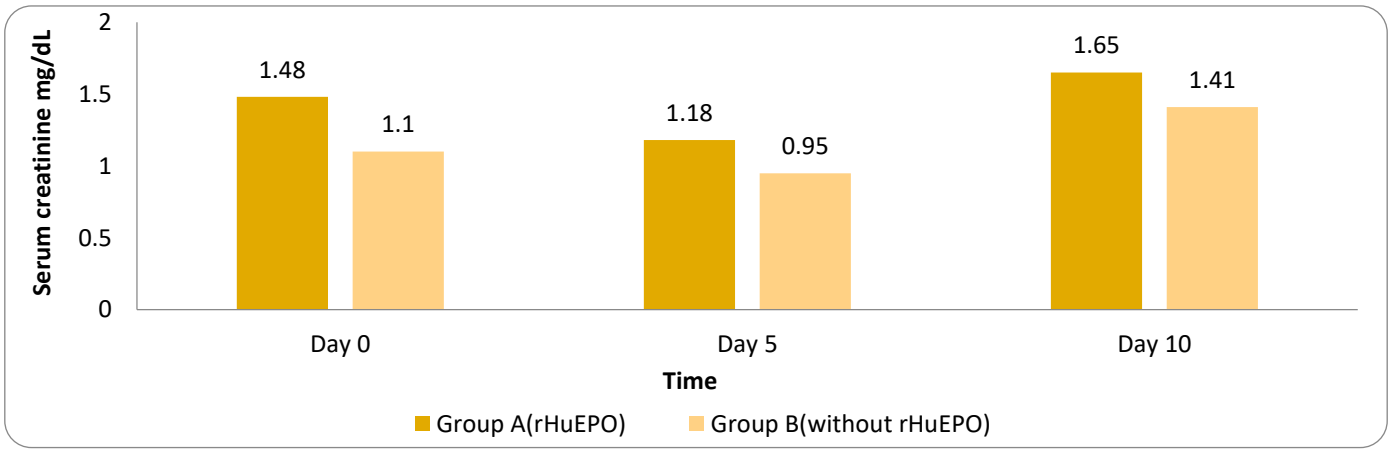

Figure 5. Mean Values of Serum Creatinine of Group A and B.

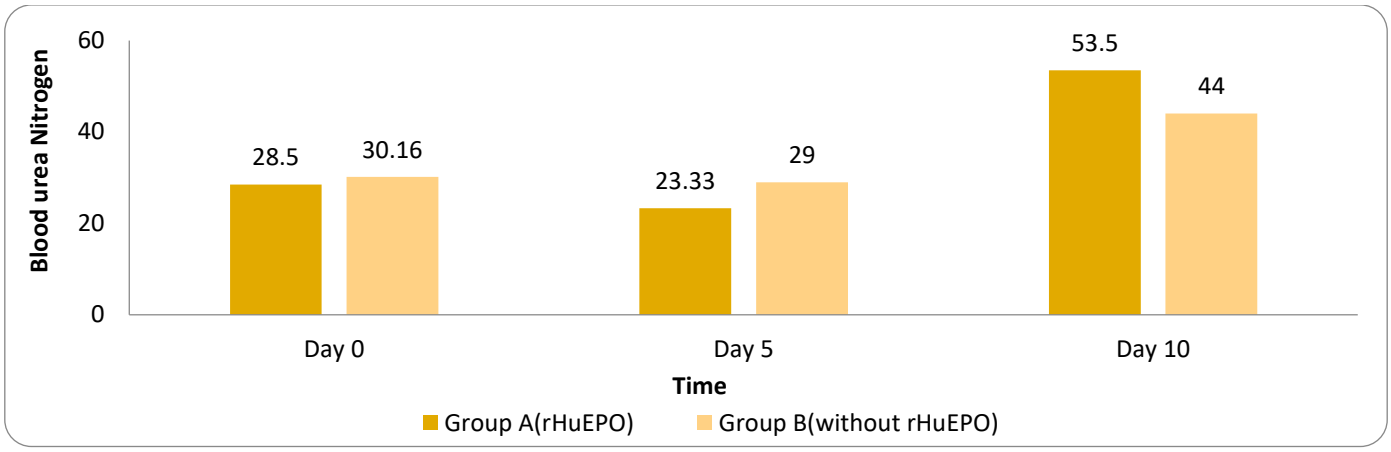

Figure 6. Mean Values of BUN of Group A and B.

DISCUSSION

RHuEPO is available commercially which can be used to initiate the process of erythropoiesis to deal with the hemato-biochemical disorders while performing nephrectomy and other surgical interventions (Flaharty et al. 1990). Moreover, no systemic effects and antigen-antibody reactions were observed during the study (Casati et al. 1987). RHuEPO can be used to improve the quality of life (Bottomley et al. 2015). Difference between Group A and B was found to be significant 0.000 (P≤0.05). There was significant increase in RBC's count at day 5^{th} and gradual increase in RBC's count on day 10^{th}due to surgical stress. MCV is associated with RBCs, its value also increased in group A as compared to group B (Urie et al. 2007). In addition to this, RBCs, hemoglobin level also increased in group A (Assarasakorn et al.2008). It was decreased in group B with a significant difference (p≤0.05). All fluctuations in value of hemoglobin were in reference range (Darby et al. 1993) (Latif et al. 2007). Mostly when the kidney function is compromised, the level of hemoglobin and PCV become lower than that of control groups.

This is because of reduction in erythropoietin (Khanamet al., 2013). While in case of group B, RBCs were reduced at day $5^{th}$and after surgery at day 10^{th} due to surgical stress. Decreases in erythropoietic stimulating factor (ESF) occur mostly after loss of renal tissues during nephrectomy. Reduction in erythropoietic stimulating factor ultimately results in decrease in RBC's production (Stenzel et al., 1975). Similarly TLC values found to be increased in group A 3.48±0.33,7.65±0.29,8.86±1.23 at day 0,5^{th} ,10^{th} respectively (p≤0.05) While in control group B, TLC also increased from 4.31±0.24, 4.31±0.17, 10.45±1.54 at day 0,5^{th} 10^{th} respectively. But this increase was not significant (Latif, et al., 2007). PCV values were found with significant difference (p≤0.05) within group A as well as in group B. A remarkable increase in PCV at day 5th and day 10th was observed in group A underwent rHuEPO. Previous studies also shown that PCV increased from 34 ± 0.7 to 44 ± 1.3% and hemoglobin from 11.3 ± 0.5 to 15.4 ± 5 g/dl in rHuEPO treated group (Perera et al., 1995). But this change was not significant with respect to reference value in group B without rHuEPO. There was remarkable increase occurred in RC after rHuEPO therapy which was 3.68±0.58 at day 0, increased at day 5th to 15.86±5.27 and further increased at day 10th up to 25.16±4.11.

After second injection of rHuEPO, values of reticulocytes increased from day 0 to 10th with a value of 4.68±1.17 to 4.88±1.12 and decreased to 3.40±0.58, respectively with P value of value of 0.000 (p≤0.05). Similarly, in previous studies, rHuEPO was used for increasing erythropoiesis in pediatric patients during the perioperative periods (Shimpoet al.,1997). Platelet counts were high in the group A as compared to B associated with erythropoietin promotion activity of thrombopoiesis (Stohlawetz et al., 2000). Blood chemistry of serum creatinine and BUN were found significant within groups (p≤0.05) as EPO was used in acute renal disorders (Sharples et al., 2006).The serum creatinine decreased at day 5th and again increased at day 10th in group A treated with rHuEPO by laparoscopic nephrectomy. Before ischemia, rHuEPO treatment was given in one group and other groups were given placebo and mannitol. Results were observed after 4 weeks. Urine creatine level was 149.1mg/dl in EPO treated dogs, while in mannitol treated 80.7mg/dl and in palacebo, it was 70.7mg/dl (Phillips et al., 2009). This rise of serum creatinine and BUN occurred after unilateral nephrectomy as burden on other kidney increased and become over functional as well due to hypertrophy. The BUN level has been recorded higher in nephrectomized group than those of controlled groups (Katsudaet al., 2014).

CONCLUSION

It is concluded that rHuEPO increases the process of erthythropoisis in rabbits underwent unilateral nephrectomy. Due to its safety, efficacy and lack of systemic side effects, rHuEPO can be used as alternate therapy of blood transfusion during performing nephrectomy or any surgical interventions. It plays effective role in the absence of one kidney to deal with the hemato-biochemical disorders.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this research.

COMPETING OF INTEREST

The authors declare no competing interests.

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