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Renal function changes in one week period following Russell's viper envenomation in rats.

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Russell's viper venom in doses of 1 and 2 mg/kg bw. was injected intramuscularly in rats weighing 250-350 gm. Renal functions were studied and compared between envenomized and normal saline injected rats at 1,6,24,72, and 168 hours. In the period of 6 hours after injection, all envenomized rats produced oliguria; moreover, some of them either developed transient anuria or died. Impaired renal functions were noted as demonstrated by azotemia and decreased renal clearance of creatinine, and significantly decreased urea nitrogen ($p < .001$). The fractional excretions of sodium and potassium of envenomed rats were enhanced in the first hour and gradually decreased until normal within 6 hours. After 24 hours, renal functions in all rats were not different throughout the experimental period.

The results of this study could be concluded that acute renal failure following Russell's viper venom injection is elucidated during the initial 6 hours with the most severity in first hour. No acute renal failure was seen in survival rats after 6 hours. However, these changes were not different between the 1 and 2 mg/kg bw. rats. Thus, it may be suggested that treatment should be given as soon as possible and should not later than 6 hours in patients envenomed by Russell's viper so as to prevent renal damage.

Key words: *Renal function, Russell's viper venom, Rats.*

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สมพล สงวนรังศิริกุล, บังอร ชมเดช. การทำหน้าที่ของไตในระยะ 1 สัปดาห์ หลังฉีดพิษงูแมวเซาเข้ากล้ามเนื้อในหนูแรท. จุฬาลงกรณ์เวชสาร 2539 กรกฎาคม; 40(7): 545-555

ฉีดพิษงูแมวเซาขนาด 1 และ 2 มิลลิกรัมต่อกิโลกรัมน้ำหนักตัวเข้ากล้ามเนื้อในหนูแรทน้ำหนัก 250-350 กรัม ศึกษาการทำหน้าที่ของไตหลังฉีด 1, 6, 24, 72 และ 168 ชั่วโมงเทียบกับหนูกลุ่มควบคุมที่ได้รับน้ำเกลือปกติปริมาตรเท่ากัน ใน 6 ชั่วโมงแรกหลังฉีด หนูที่ได้รับพิษงูทั้งสองขนาดทั้งหมดมีการขับถ่ายปัสสาวะลดลง หนูบางตัวไม่ถ่ายปัสสาวะเลยชั่วระยะเวลาหนึ่งหรือบางตัวเสียชีวิตไป ไตทำหน้าที่ลดลงโดยตรวจพบความเข้มข้นของครีเอตินินและยูเรียในโคโรเจนได้ลดลงอย่างมีนัยสำคัญทางสถิติ ($p < .001$) สัดส่วนการขับถ่ายต่ออัตราการกรองโซเดียมและโปแตสเซียมเพิ่มขึ้นในหนูกลุ่มที่ได้รับพิษงูในระยะเวลาชั่วโมงแรกแล้วกลับลดลงจนเป็นปกติใน 6 ชั่วโมง หลังจาก 24 ชั่วโมง การทำหน้าที่ของไตแตกต่างจากกลุ่มควบคุมจนสิ้นสุดการทดลอง

ผลการทดลองครั้งนี้สรุปได้ว่าภาวะไตล้มเหลวเฉียบพลันจากงูแมวเซาเกิดขึ้น และมีอันตรายมากในชั่วโมงแรก และเกือบเป็นปกติใน 6 ชั่วโมงหลังฉีด หนูที่มีชีวิตรอดหลัง 6 ชั่วโมงไม่พบมีภาวะไตล้มเหลวเฉียบพลัน อย่างไรก็ตามการเปลี่ยนแปลงที่เกิดขึ้นจากพิษงู 2 ขนาดทดลองไม่มีความแตกต่างกัน ดังนั้นจึงอาจเสนอแนะได้ว่าควรให้การรักษาผู้ป่วยถูกงูแมวเซากัดโดยเร็วที่สุดเท่าที่จะทำได้ และไม่ควรเกิน 6 ชั่วโมงหลังถูกกัดเพื่อป้องกันไตถูกทำลาย

Russell's viper bite is one of the more important causes of acute renal failure in tropical countries.^(1,2) Acute tubular necrosis was seen in renal biopsies and autopsy specimens of human victims;^(2,3) rabbits^(2,4) and also mice and rats.⁽²⁾ Russell's Viper venom (RVV) contains potent procoagulants that activate factor V and X that produces the clinical picture of acute disseminated intravascular coagulation.^(5,6)

Hypotension can cause the sudden decrease in renal blood flow which may indicate ischemic renal failure. However, renal failure has been noted in some cases of Russell's viper bite without hypotension thus indicating indirect nephrotoxicity.⁽⁷⁾ However, the direct nephrotoxic effect has been reported by some investigators.^(4,8,9)

In animal models, renal function changes have been demonstrated only in the earlier period.^(10,11) This study has been posted to illustrate the renal changes in a longer period of time.

Materials and Methods

Experiments were performed on 100 Wistar rats weighing 250-350 grams. These were divided into 3 groups and 5 periods of study of 1,6,24,72 and 168 hours postinjection. For each time period, 4 control rats were injected intramuscularly with normal saline while lyophilized crude venom of Russell's viper *siamensis* (RVV) at 1 and 2 mg/kg-bw was injected in each group of 8 experimental rats. Urine flow rate and heart blood were collected for study of the renal functions.

Thirty minutes before study time, each rat was anesthetized with inactin at 100 mg/kg-bw

intraperitoneally. High pressure polyethylene tube was introduced into the urinary bladder by surgical incision on the linear alba for measuring the urine flow rate and for collection of urine. Fifteen minutes was allowed for stabilization, and the urine flow rate and urine collection were done over about a 20 minute period. All of the cardiac blood was collected for measuring renal functions.

Measurements of creatinine, urea nitrogen, and sodium and potassium concentrations in the urine and plasma were determined by Jaffy reaction as reported by DiGiorgio, 1974,⁽¹²⁾ Morin and Prox, 1973⁽¹³⁾ and KLiNa flame operating Beckman Instrument model 343, respectively.

At the end of the experiment, the kidneys were excised, stripped of surrounding fat and tissue, blotted dry and weighed so that the urine flow rate, plasma clearance of creatinine and urea could be expressed as per gram kidney weight.

Renal functions were compared between the saline control rats and RVV injection rats for the same period of time. The results are shown as the value of mean + SEM. The differences were analyzed by the Student's unpaired t-test with statistically significant difference of $p < .05$

Results

Figure 1: effect of RVV on mean \pm SEM of plasma creatinine (P_{cr}).

Plasma creatinine concentration was markedly increased in the 6 hour period after venom injection. After 24 hours this change was very little different from the saline group. However, the variation of plasma creatinine

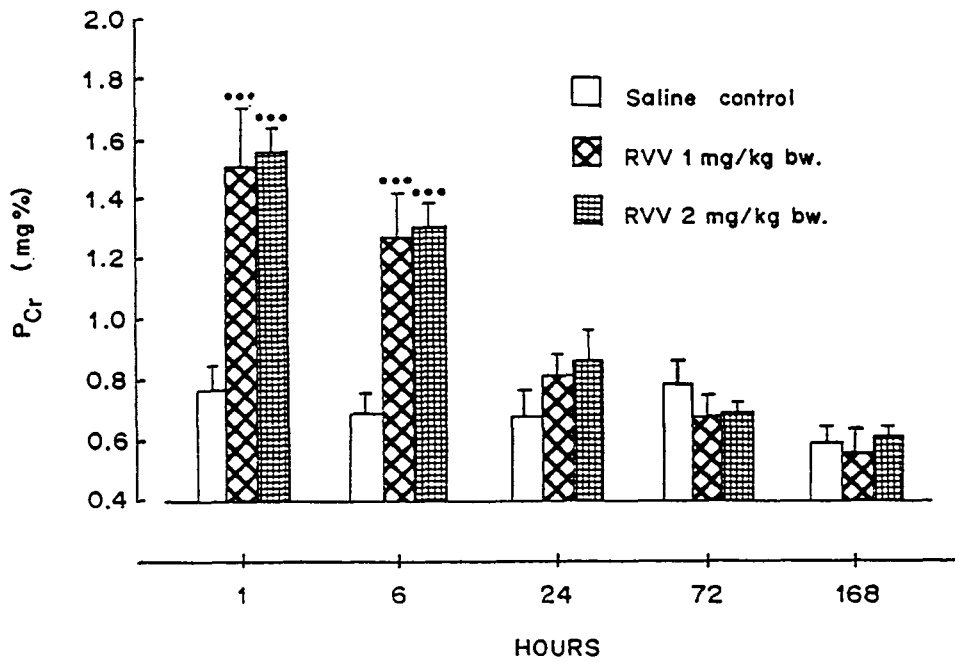


Figure 1. Effect of RVV on mean \pm SEM of plasma creatinine (P_{cr}). .p<05,..p<01,..p<.001

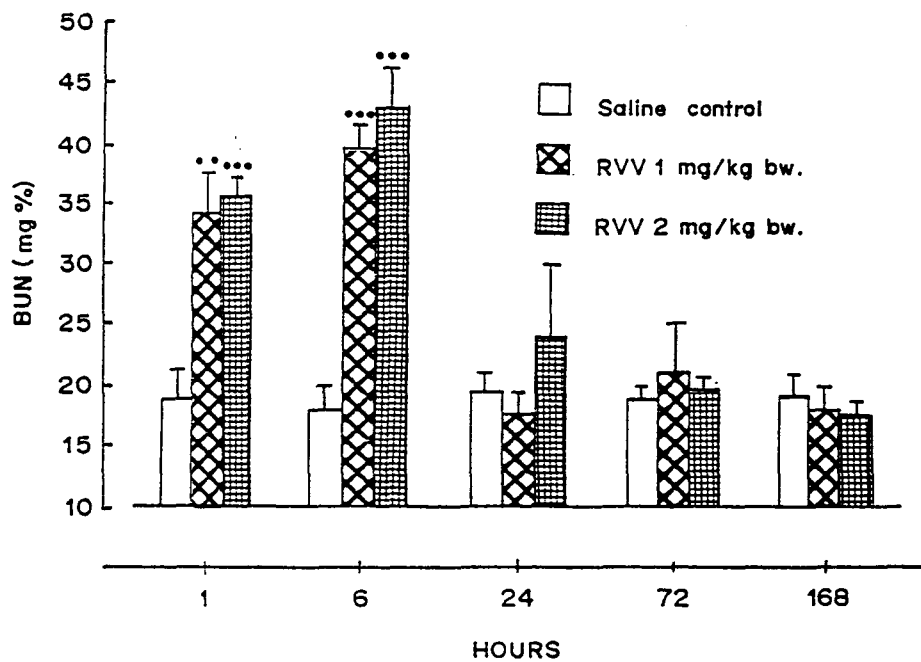


Figure 2. Effect of RVV on mean \pm SEM of blood urea nitrogen (BUN). .p<05,..p<01,..p<.001

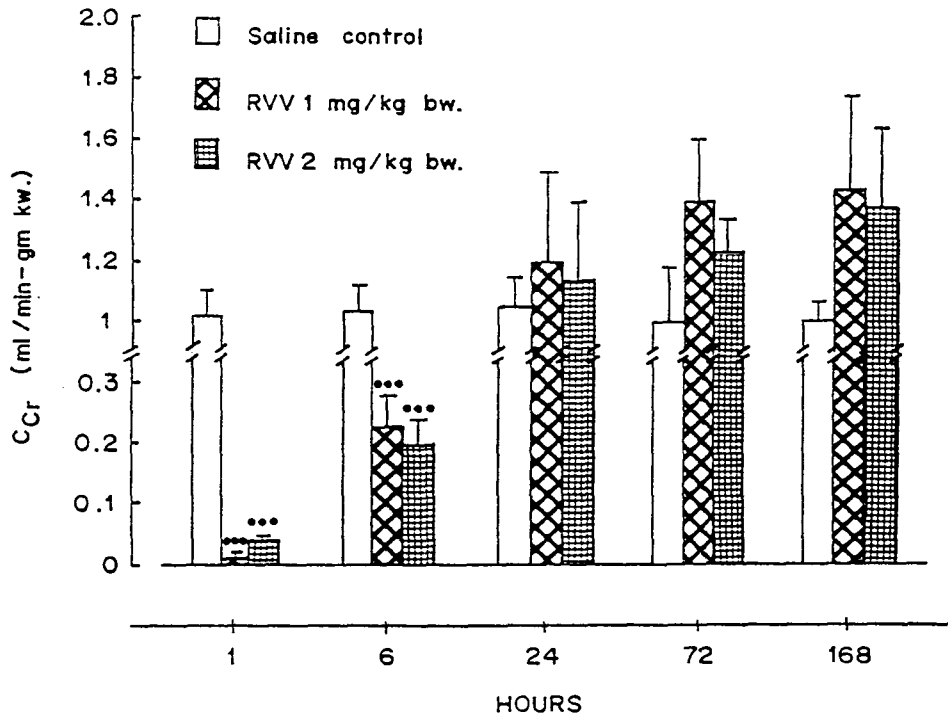


Figure 3. Effect of RVV on mean \pm SEM of plasma clearance of creatinine (C cr). .p<05,...p<01,...p<.001

concentrations were not statistically significantly different between the two doses of experimental groups.

Figure 2: effect of RVV on mean \pm SEM of blood urea nitrogen (BUN).

Injection of Russell's viper venom significantly enhanced blood urea nitrogen. The change was more severe at 6 hours post-venomation. At the 24 hour period, higher concentrations of BUN in some 2 mg/kg-bw rats was seen.

Figure 3: effect of RVV on mean \pm SEM of plasma clearance of creatinine (C cr).

Plasma clearance of creatinine was very low following venom injection, especially after the first hour period. After 6 hours plasma clearance of creatinine was restored and reached normal levels in 24 hours. After 24 hours there

was a continued increase in plasma clearance of creatinine but this was without statistical significance throughout the experimental period.

Figure 4: effect of RVV on mean \pm SEM of plasma clearance of urea (C urea).

Plasma clearance of urea was decreased significantly in the period of 6 hour post-venomation. After 24 hours, significantly augmented plasma clearance of urea was seen. After 24 hours the plasma clearance of urea fell to normal levels until the end of experiment.

Figure 5: effect of RVV on mean \pm SEM of urine flow rate (V).

Russell's viper venom produced anuria or some oliguria in the 6-hour period when compared to the saline control rats. At 24 hours, 1 mg/kg-bw envenomated rats produced significant polyuria. Urine flow increased throughout

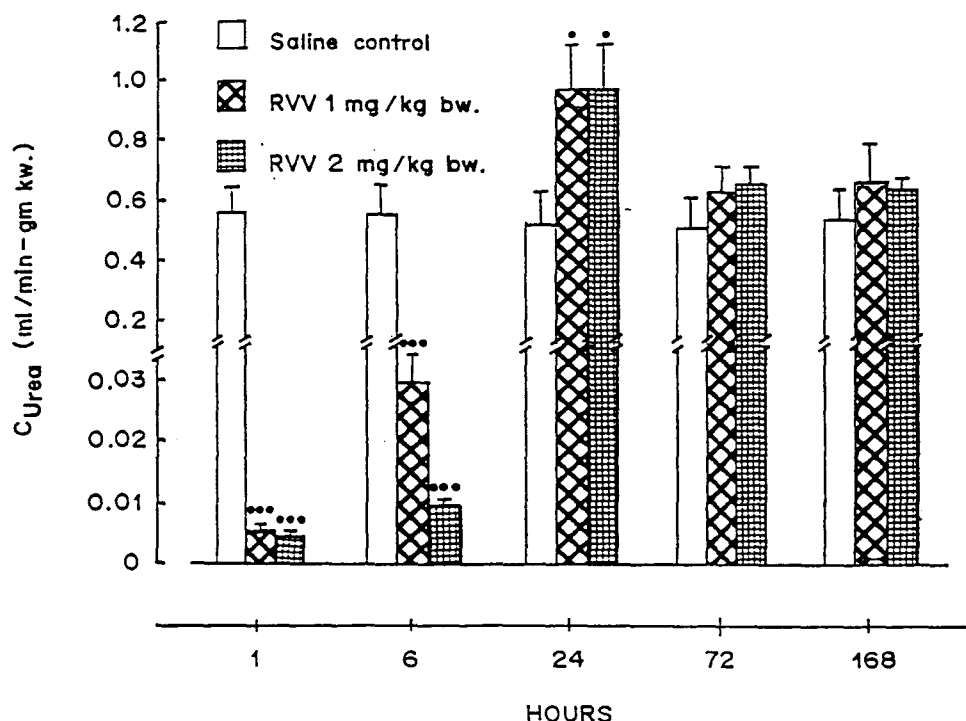


Figure 4. Effect of RVV on mean \pm SEM of plasma clearance of urea (C_{urea}). .p<05,..p<01,..p<.001

the 24-hour experimental period but was statistically insignificant when compared with the saline control rats.

Figure 6: effect of RVV on mean \pm SEM of fractional excretion of sodium (FENa).

Fractional excretion of sodium was significantly enhanced after the 1-hour period and then declined to normal levels at 6 hours. At 24 hours fractional excretion of sodium went up significantly in the 1 mg/kg-bw rats. After 24 hours there were not any differences of fractional excretion of sodium in all groups of rats.

Figure 7: effect of RVV on mean \pm SEM of fractional excretion of potassium (FEK).

RVV raised the fractional excretion of potassium significantly during the 1-hour period and declined to normal levels at 6 hours There was a slight increase in fractional excretion of

potassium again at 24 hours but after 24 hours there was no difference of fractional excretion of potassium in all groups of rats.

Discussion and Conclusions

Major causes of death after Russell's viper bite include acute renal failure, circulatory collapse and intracranial or massive gastrointestinal bleeding, but of all these, renal failure is the most frequent.^(1,2,6,14) RVV contains a number of powerful procoagulant enzymes.⁽⁵⁾ These haemostatic disturbances may be responsible for death or organ/tissue damage both through hemorrhage and microvascular occlusion by fibrin thrombi.

Alterations of circulatory hemodynamics by RVV have been believed to effect the renal functions.^(10,15) Correlation of renal function

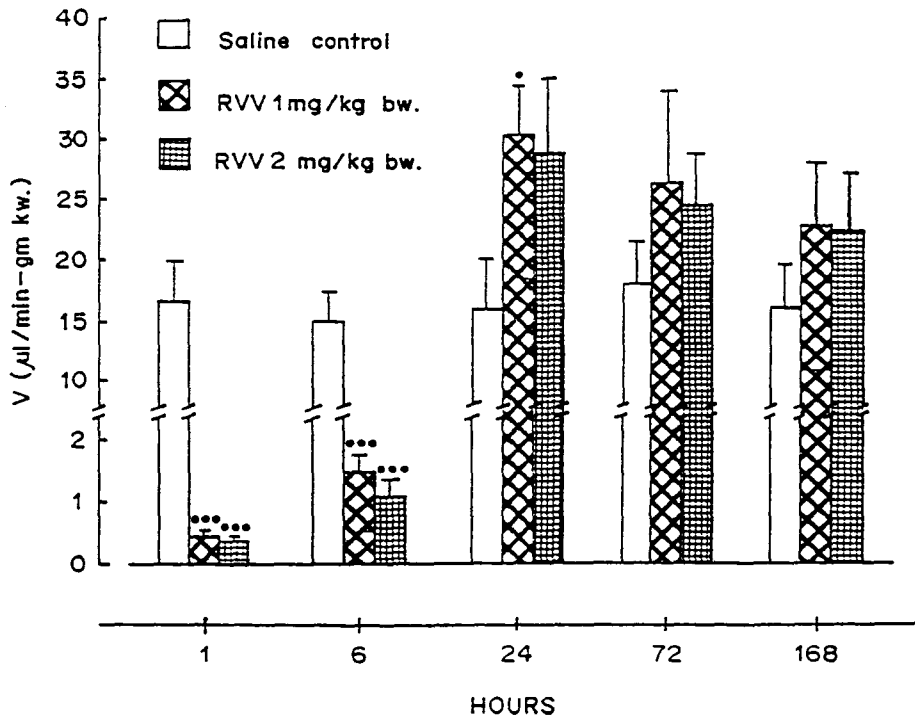


Figure 5. Effect of RVV on mean \pm SEM of urine flow rate (V). .p<05,..p<01,...p<.001

changes following hemodynamic alterations have been demonstrated. However, animal studies have been reported as 2 days post injection. Renal hemodynamics and renal functions have been suddenly and continually reduced after venom injection. The maximum effect has been during the first hour accompanied with slight increases in fractional excretion of electrolytes.⁽¹⁰⁾ A marked but transient increase in glomerular capillary permeability in victims of Russell's viper bite in Myanmar⁽¹⁶⁾ has been reported. Albuminuria was found in patients who became systemically envenomed. It was associated with high fractional sodium excretion with acute oliguric renal failure. The same changes have been demonstrated in experimental rats.⁽¹⁷⁾

Some reduced renal functions lasted as long as 6 hours as demonstrated in our inves-

tigation. Further rises in blood urea nitrogen (Fig.2) with high plasma concentrations of creatinine (Fig.1), whereas low renal clearances were also shown (Figs. 3,4). The responses were not different between 1 and 2 mg/kg-bw envenomed rats. Failure of the kidneys to excrete urine during this period has also been illustrated (Fig. 5).

At 24 hours, almost all renal functions were restored to normal levels. Rats who received 1 mg/kg-bw envenomation exhibited polyuria, while fractional excretion of sodium and potassium increased significantly (Figs. 5,6,7). After 24 hours, all surviving rats showed no evidence of abnormal hematological changes. All renal function tests from this investigation were not statistically significantly different from the saline control rats.

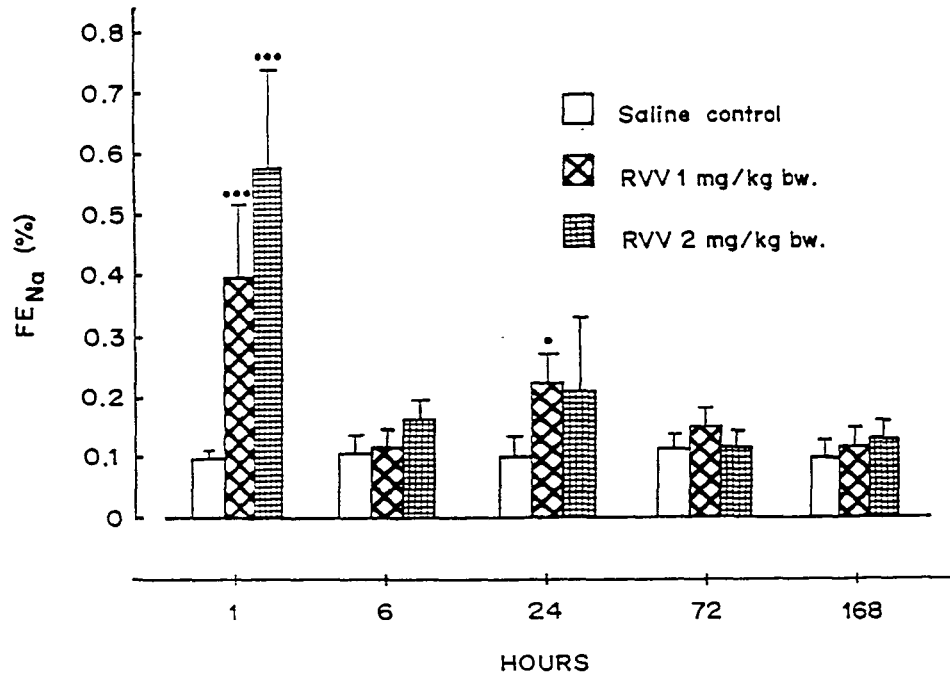


Figure 6. Effect of RVV on mean \pm SEM of fractional excretion of sodium (FENa). .p<05,..p<01,...p<.001

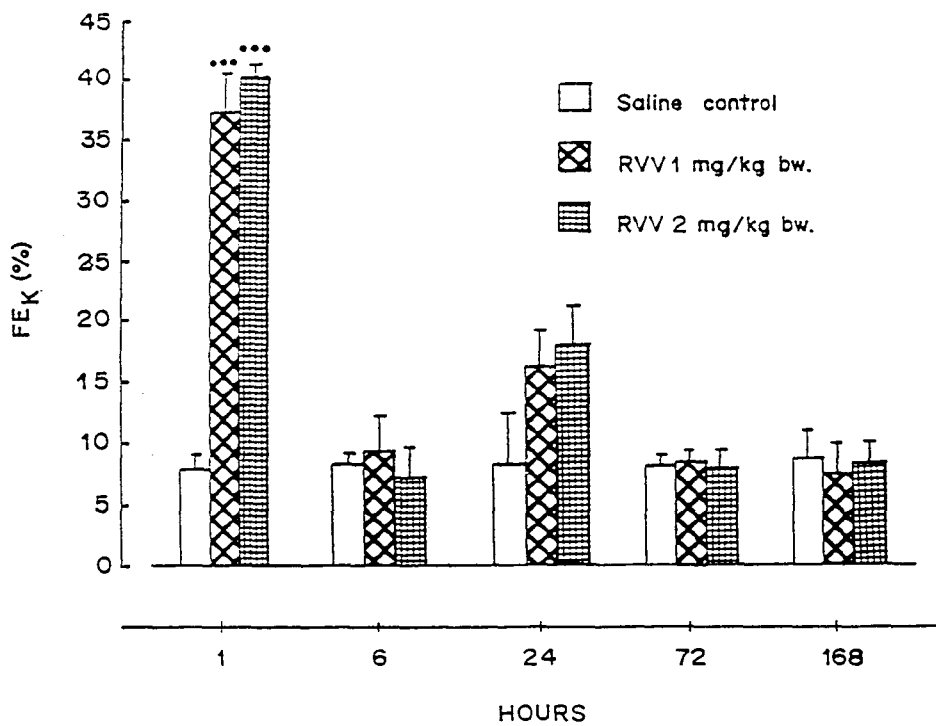


Figure 7. Effect of RVV on mean \pm SEM of fractional excretion of potassium (FEK). .p<05,..p<01,...p<.001

In our study acute renal failure was demonstrated in the first 6 hours by oliguria and an increase in plasma concentrations of creatinine and blood urea nitrogen.(Figs.1,2) In addition, there was also a reduction of glomerular filtration rates as revealed by renal clearance of creatinine and urea nitrogen.(Figs. 3,4)

Renal ischemia has been believed to be the cause of important pathophysiological changes from RVV envenomation⁽¹⁸⁾ since gradual decreases in arterial pressure have been demonstrated following envenomation in animals.^(15,17)

Tin-Nu-Swe, et al (1993) reported very high plasma renin in patients after Russell's viper bite and suggested that the renal ischemia is an important pathophysiological component. Renal tubular damage and dysfunction could have resulted from ischemia in the development of acute renal failure.

The situation is complex because elevation of plasma renin could be a cause, or a consequence, or both renal ischemia and acute renal failure. Failure of renal hemodynamics by RVV envenomation appeared to be mediated by an increase in the level of endogenous angiotensin II, since pretreatment of angiotensin I converting enzyme inhibitor was found to improve⁽¹⁹⁾ the condition.

It has been shown that renal autoregulation of blood flow was maintained following injection of RVV in dogs.⁽¹¹⁾ Renal vasodilator prostaglandin is believed to play a significant role in the modulation and maintenance of renal blood flow. Activation of the the renin-angiotensin system could be due to stimulation of prostaglandin production.

The results obtained from this study clearly showed that renal functions are depressed by RVV during the first 6 hour postenvenomation. The most depression of renal functions occurred in the first hour and then they gradually improved. After 24 hours normal renal functions were demonstrated in all of our surviving rats.

After 6 hours post-injection, some rats developed diuresis concomitant with increased plasma concentrations of creatinine and blood urea nitrogen. (Figs 1,2) It should be said that renal functions determined from patients after 6 hours of envenomation showed nonoliguric renal failure as report by Anderson et al, 1977.⁽²⁰⁾

From our observation in the period of first hour all rats which received either 1 mg or 2 mg/kg-bw exhibited oliguria and some anuria with a 25% death rate. Sixty percent had hematuria and half of them bled from the nose and mouth. These changes were not significantly different between the two experimental groups. The mechanism of venom on the kidneys is most likely indirectly caused by circulatory hemodynamic changes since renal functions were similar in both groups of rats.

From this study it may be suggested that nephrotoxicity from RVV developed during the first 6 hours after the bite. To avoid such devastating effects on the kidneys, antivenom or parenteral fluid treatment has to be given very early in the treatment of envenoming.

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