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Renal Histopathology, Blood Urea Nitrogen and Creatinine Levels of Rats With Unilateral Ureteral Obstruction

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Abstract

Ureteral obstruction is an urinary tract disorder that can occur in animals and humans. The effect of total unilateral ureteral obstruction on the kidneys is fatal if not immediately treated because it can cause ipsilateral or contralateral kidney damage. This study was conducted to determine renal histopathological features, and blood urea nitrogen (BUN) and creatinine levels in white rats that had a unilateral ureteral obstruction. Thirty-six 2,5 months female Sprague Dawley rats were divided into 3 groups. Group I (control) was operated laparotomy. Group II was operated by ligating the right ureter in the proximal part. Group III was operated by ligating the right ureter in the distal part. One week after ligation three rats were taken randomly from each group and their blood was taken for BUN and creatinine analysis. The right and left kidneys were taken to make histopathological preparations. The same treatment was carried out at 2nd , 3rd , and 4th weeks after surgery. Statistical analysis showed an increase in BUN and creatinine. Macroscopically, ipsilateral renal hydronephrosis occurs from the first week after unilateral ureteral ligation, which is characterized by renal pelvic dilatation, parenchymal depletion, vacuolization and fluid deposits in the right kidney. The ipsilateral renal histopathology examination showed glomerular atrophy and tubular dilatation in the first week after ligation. Cysts formation and interstitial fibrosis occurred on the 2nd to 4th week of the ipsilateral kidney and getting worse along with the length of obstruction time. Compensatory reaction occurred in the contralateral kidney was found with dilatation of tubulous distal and proximal from the first week after ligation. This study showed that unilateral ureteral ligation in the proximal and distal regions causes an increase in BUN and creatinine and hydronephrosis of the ipsilateral kidney which appears macroscopically and histopathologically. Ipsilateral renal hydronephrosis occurs from the first week after unilateral ureteral ligation, which is characterized by pelvic renal dilatation, parenchymal depletion, vacuoles formation, and fluid deposits in the kidneys. Histopathologically, ipsilateral renal damage characterized by glomerular atrophy, inflammatory response, vacuolization, and fibrosis. Contralateral compensatory response characterized by dilatation of the tubulous convulatus and collecting ducts.

Key words; ureteral obstruction; kidney; blood urea nitrogen; creatinine; histopathology

Introduction

Urinary tract obstruction in animals includes the occurrence of proximal urinary tract obstruction (renal pelvis and ureter) as well as the distal urinary tract (vesica urinaria and urethra) (Rowse, 2003). In general, urinary tract obstruction can occur in human and animals, and has the potential to cause death if not treated properly. Urinary tract obstruction is generally accompanied by infection, although some cases have no signs of infection (Shipov and Segev, 2013; Tucci et al., 1997). In young animals, obstruction is usually caused by congenital factors such as atresia or urinary tract stenosis, whereas in older animals obstruction is usually caused by tumors, cancer, or calculi (Lim et al., 2013; Trnka et al., 2012).

Urolith is one of the main causes of urinary tract obstruction. The prevalence of proximal

urinary tract obstruction in dogs and cats due to urolithiasis is 5%, whereas in the distal urinary tract is 95% (Stevenson, 2002). Makhdoomi and Gazi (2013) reported that the incidence of urinary tract obstruction due to urolithiasis in buffalo was 81.25%, cattle 8.92%, sheep 1.04%, goats 49.83%, and horses 1.38%. The incidence of ureteral obstruction is most common in cats. This is due to the very small size of the ureteral lumen, which is only $\pm$0.4 mm (Kochin et al., 1993). The incidence of ureteral obstruction in cats has increased dramatically in the last decade (Cannon et al.,2007). The high incidence of urolithiasis which causes ureteral obstruction is one of them, due to the feed factor consumed. Calcium-phosphorus ratios imbalance, high level of protein and oxalate can cause an increase minerals concentration that form calculi and changes urine pH (Stevenson, 2002).

Ureteral obstruction can also occur in the connecting channel between the renal pelvis and the ureter or ureteropelvic junction (proximal ureter) and at the border between the ureter and vesica urinaria or ureterovesicular junction (Fischer et al., 2009). These two cases can occur due to congenital factors such as lumen stenosis, presence of calculi, and torsion caused by trauma. (Kausik and Segura, 2003). Diagnosis must be made as early as possible because the longer the blockage time will reduce the success of therapy, and more difficult to return kidney to normal function (Segev, 2011). Ureteral obstruction can be located in the proximal (ureteropelvic junction) or in the distal part (ureterovesicular junction). The two locations of obstruction will have different effects on the kidneys and require different treatment, so the location must be known before surgery (Decramer et al., 2007).

Blood urea nitrogen (BUN) describes the number of nitrogen atoms in the blood that are combined with urea (Lane and Cooper, 2003). Urea is filtered freely in glomerulus and reabsorbed in the renal tubules. The urea reabsorption in the collecting duct is mediated by arginine vasopressin (AVP) (Schrier, 2008). Laboratory analysis of BUN and urea can be used as parameters to describe kidney function. In general, an increase in BUN is associated with a decrease in glomerular filtration rate (GFR). Creatinine is a by-product of muscle metabolism which will be freely filtered by glomerulus, and not reabsorbed by the renal tubules. Some species secrete creatinine through tubules, except in dogs (Cunningham and Klein, 2007). Blood creatinine and BUN will increase when the patient is dehydrated (pre-renal azotemia), but the increase in these two parameters can also indicate kidney problems (Lane and Cooper, 2003). The purpose of this study was to determine the development of kidney damage histopathologically and the effects of kidney damage on BUN and creatinine levels.

Materials and Methods

This study used 36 female Sprague Dawley rats, 2.5 months old, 150-200 grams. The research was carried out in the experimental laboratory of the Department of Surgery and Radiology, Faculty of Veterinary Medicine, Universitas Gadjah Mada (UGM). The use of experimental animals in this study has been approved by the Ethical Commission of the Integrated Research and Testing Laboratory UGM with registration number 437 / KEC-LPPT / III / 2016.

Rats were adapted for one week, given standard feeds (normal proteins, fats and carbohydrates) and were given *ad-libitum* drinking water. The rats were then divided into 3 groups randomly, each group consist of 12 rats. The surgery uses a combination of ketamine (80 mg / kg body weight) and xylazine (10 mg / kg body weight) as the anesthesia agent. Group I was used as the control, treated with laparotomy and then closed back without organ manipulation. Group II was the group receiving laparotomy treatment followed by ligation of the right ureter in the proximal part, 5 mm from the renal pelvic with surgical silk suture, then the abdominal cavity was closed. Group III was treated with laparotomy, followed by ligation of the right ureter in the distal part, 5 mm from vesica urinaria with surgical silk suture, then the abdominal cavity was closed. One week after surgery, 3 rats were taken from each group randomly, euthanized and kidneys were taken from the body. The right and left kidneys are then stored in tubes containing 10% formalin to make histopathological preparations. The same treatment was carried out at 2nd , 3rd , and 4th weeks postoperative.

Blood samples were taken on the 1st, 2nd, 3rd, 4th week after surgey, through the medial canthus before euthanasia was performed, using microhematocrit and accommodated in tubes containing EDTA anticoagulants. Samples were examined in the UGM Animal Hospital for BUN and creatinine examination. Data were analyzed statistically using analysis of variant 3x4 factorial pattern. The histopathology result were analyzed descriptive-comparatively by looking at changes in the right and left kidney.

Results and Discussion

Kidney histopathology on the first week after ligation

Microscopically, right proximal and distal tubules of the right kidney dilated on the first week after ureteral obstruction. Mild dilation occurs in Group III, whereas severe dilation and tubular epithelium depletion occur in Group II (Figure 1). Glomerular atrophy occurs in the cortex but the nephron is still dominated by active glomerulus which has a normal shape and structure. Debris appears in the lumen of distal convulatus tubules. Renal corpuscles damage due to obstruction is characterized by glomerular atrophy and widening of Bowman's space (Radovic et al., 2014). Widening of the afferent arterioles appear in Groups II and III. Afferent arterioles dilated to maintain hemodynamic pressure and renal GFR (Canton et al. 1979). Collective ducts in the medulla region are dilated. Neutrophil infiltration was found in the Group II ducts.

Microscopic observation of Group II left kidney showed that the cortex was in good

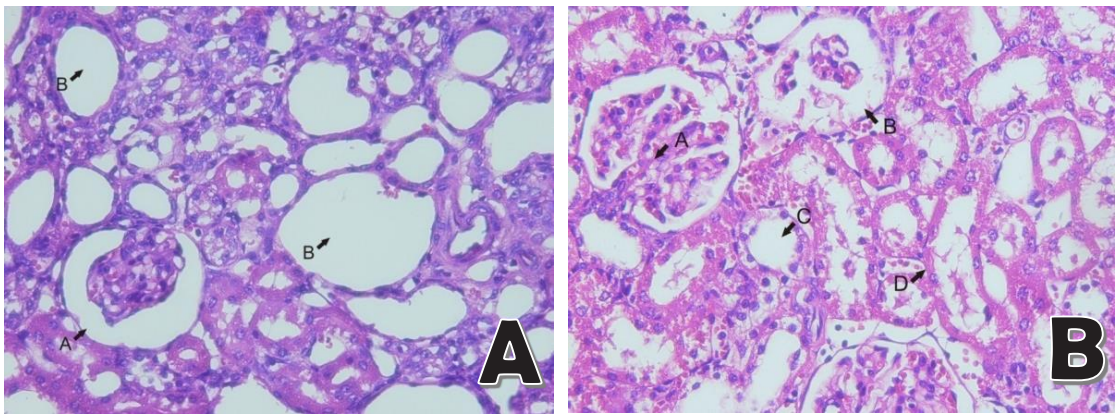

Figure 1. **A.** Histopathology of Group II right kidney. Glomerular atrophy and widening of Bowman's space (A), Tubular dilatation forms cyst (B) (HE stain x 40 objective). **B.** Histopathology of Group III right kidney (distal ureteral ligation) in the first week. Normal glomerulus (A), glomerular atrophy (B), lumen dilatation of distal convulatus tubules (C) lumen dilatation of proximal convulatus tubules (D) (HE stain x 40 objective).

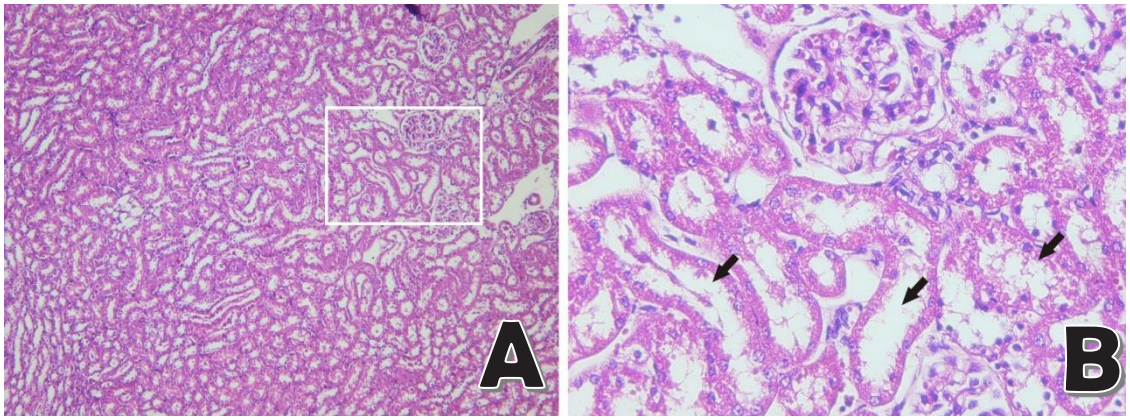

Figure 2. Histopathology of Group III left kidney (distal right ureteral ligation) on the first week. Mild dilatation occurs in the proximal and distal tubules in the cortex (the dilated zone is shown by an arrow) (A. HE stain, x 4 objective; B. HE stain x 40 objective)

condition, dominated by glomerulus with normal shape and structure. The Bowman capsule epithelium still looks good with two thin cell layers, the parietal layer on the outside and the inner visceral layer. Bowman's space was not dilated. Lumen dilatation did not occur in the proximal and distal convex tubules. Microscopic changes are seen in the Group III left kidney (right distal ureteral ligation). Mild dilatation of the proximal and distal tubular lumen is found in the cortex. Proximal convulate tubular epithelium appears to be depleted but microvilli is still visible (figure 2). Unilateral ureteric obstruction causes a variety of morphological and pathophysiological changes in the ipsilateral renal parenchyma (Radovic et al., 2014).

Kidney histopathology on the 2nd week after ligation

Macroscopically, on the second week after ligation parenchymal depletion occurs in the right kidney of group II. Distal convulatus tubules are dilated creating distance between glomerulus. Cysts are bigger than in first week, tubular epithelium are depleting. Glomerular athrophy increases, characterized by shrinking corpuscles and glomerulus. The bowman's space become wide and the capsule epithelium are depleting. In the medulla, the collecting ducts are atrophy and the lumen is narrowed to the distal part, but the proximal is dilated. The Group III right kidney is inflamed which is dominated by neutrophil cells in the interstitial tissue (Figure 3). Glomerulus undergoes atrophy accompanied by the size of the corpuscule which also shrinks.

Second week after ligation, the histological structure of the Group II and III left kidney appeared normal. In the cortex, glomerulus looks normal in shape and size. Bowman's capsule looks normal, with a normal Bowman space. Urethral obstruction causes infiltration of monocytes / macrophages in the ipsilateral kidney. Inflammatory cell infiltration in the tubulointerstitial area is observed in various forms of chronic renal impairment, and persistent inflammation of the kidney will continue to become tubulointerstitial fibrosis and decrease kidney function (Wu et al., 2010). A decrease in the number of ipsilateral renal glomeruli occurs from the 14th day after ureteral obstruction. Acute phase of ureteral obstruction will develop into tubular apoptosis. In this phase, renal tubular epithelial cells die because of the stimuli from TGF-β1 and TNF-α (Tornhill et al., 2005).

Kidney histopathology on the 3rd week after ligation

Third week after ligation, parenchymal depletion occur in the right kidney of Group II as well as Group III. Tubular dilatation creates bigger cysts in the medulla. Fibroblasts are found in the cortex around glomerulus, tubules, and arterioles in Group III (Figure 4). Bowman's space dilated,

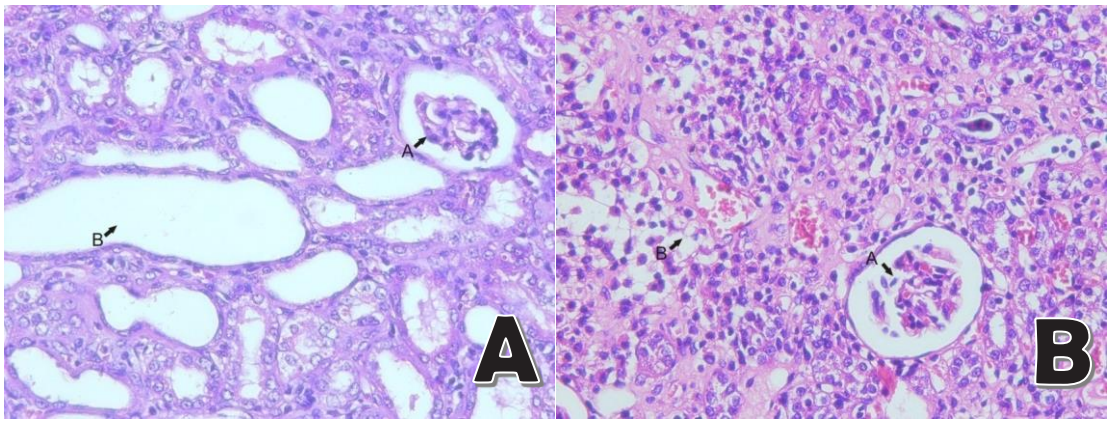

Figure 3. **A.** Histopathological change of Group II right kidney (proximal right ureteral ligation) on the 2nd week. Glomerular atrophy (A), dilated proximal convulatus tubules accompanied by thinning of the tubular epithelium and form a cyst (B). **B.** Histopathology of Group III right kidney (distal ureteral ligation) on the 2nd week. Glomerular atrophy and the Bowman space are widened (A), tubular necrosis (B), inflammatory cells spread on interstitial tissue (HE stain x 40 objective).

infiltration of neutrophils and lymphocytes is found in the collective ducts and distal tubules. Right kidney of group II has tubular atrophy and cysts that dominate renal cortex. Fibrosis occurs in the interstitial tissue between the medullary collecting ducts. The shape of the papilla cannot be recognized (figure 1). Neutrophil infiltration is found in the lumen of the collecting duct. The causative factor for interstitial fibrosis is epithelial-mesenchymal transformation, which is the transformation of renal tubular cells into fibroblasts (Chevalier et al., 2009). Chronic unilateral ureteral obstruction will cause accumulation of collagen or extracellular matrix: fibrosis, sclerosis and scarring process. The process is a maladaptative response to kidney damage, which should be a process of wound healing.

The Group II left kidney still has a good parenchymal structure. Nephrons still look compact, with normal cortical and medullary structures. Glomerular atrophy is not found. Proximal and distal convulatus tubules appear normal, do not experience dilatation or epithelial changes. Group III left kidney appears to have tubular dilatation in the cortex and medulla. The proximal convex tubular lumen is dilated accompanied by epithelium depletion. Some tubules have lost microvilli. Dilation also occurs in the collecting duct in the medulla (Figure 5). The cortex also found afferent arterioles with congestion. The shape of the papilla still looks normal. Damage of one kidney will cause changes in blood pressure and GFR. Changes in blood pressure and the amount of blood entering

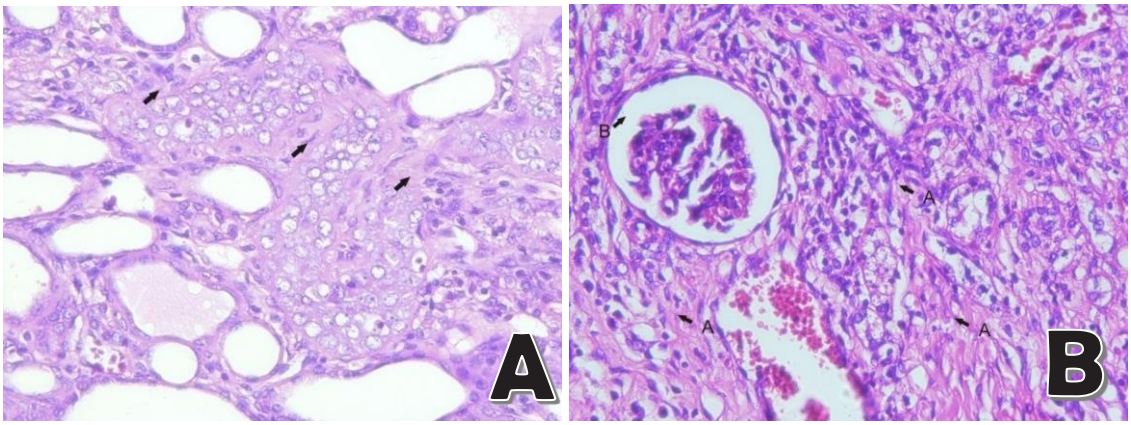

Figure 4. **A.** Histopathology of Group II right kidney (proximal right ureteral ligation) 3rd weeks. Interstitial fibrosis (fibroblast are shown by black arrow). **B.** Group III Histopathology right kidney (distal right ureteral ligation) 3rd weeks. Interstitial fibrosis (A), inflammation and bowman's space dilatation (B) (HE stain x 40 objective).

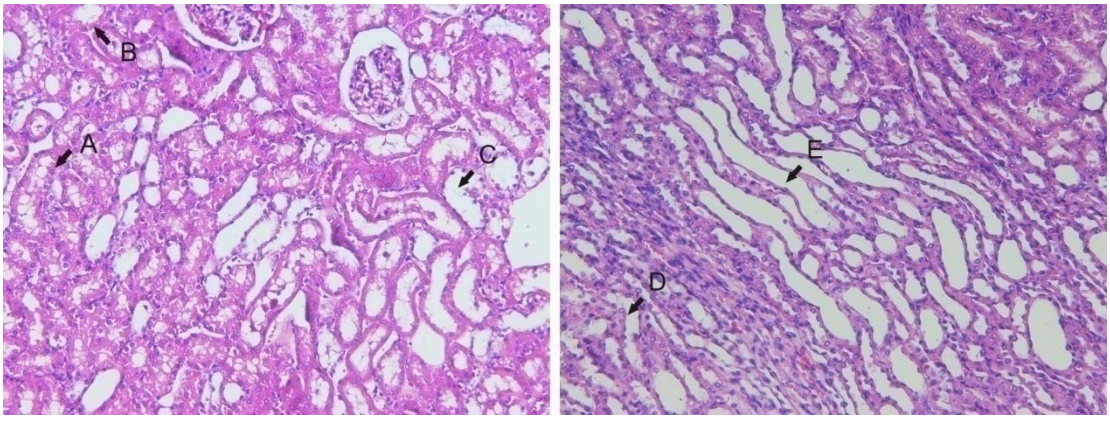

Figure 5. Histopathology of left kidney group III (right distal ureteral ligation) 3 weeks. Proximal convulatus tubules are normal (A), normal distal convulatus tubules (B), mild tubular dilatations accompanied by epithelial depletion (C), normal collecting ducts (D), collecting ducts have dilatation and thinning of the epithelium (HE stain x 10 objective)

the kidneys will affect the radial arteries of the cortex and afferent arterioles. When an increase or decrease in blood pressure, arterioles will respond with vasoconstriction and vasodilation, maintaining blood flow to the glomerulus. This mechanism is called kidney auto regulation. An increase in GFR will cause an increase in urine formation (Rhoades and Tanner, 2003).

Kidney histopathology 4th week after ligation

Entering the 4th week after ureteral ligation, the Group II right kidney perenchymal thinning (Figure 6). The boundary between the outer and inner medulla is difficult to distinguish. Fibrosis occurs in the cortex and medulla. Tubular dilation forms multiple cysts in the cortex. The tubular epithelium experiences thinning and atrophy. 4th post-ligation there are many degenerative changes in the obstructed kidney. At the boundary between the lumen and the kidney parenchyma there is a process of necrosis (Forbes et al., 2013). Group III right kidney experienced parenchymal depletion in the 4th week after ligation. The vacuole formed as a result of fluid accumulation in the kidneys causes the parenchyma to stretch. Kidney papillary and hilum are nowhere to be seen. Interstitial fibrosis occurs in the medulla, between the collecting duct. In the cortex, tubular dilation is found and form larger cysts.

Although there is a decrease in the number of glomeruli up to 50% in the ipsilateral kidney, the contralateral kidney does not experience a decrease in the number of glomeruli (Tornhill et al., 2005). Ureteral obstruction causes infiltration of monocytes/ macrophages. Infiltration of inflammatory cells is also found in chronic kidney disorders. Persistent inflammation process can cause tubulointerstitial fibrosis and decrease function of it (Wu et al., 2010). Interstitial fibrosis and tubular apoptosis occur in the obstructed renal medulla. The process of interstitial fibrosis and tubular apoptosis in obstruction without infection occurs slowly but progressively. Interstitial fibrosis is the final stage of chronic kidney damage (Radovic et al., 2014). Microscopic observations of Group II and III left kidney at week 4 showed that the cortex was still in good condition, dominated by glomerulus with normal shape and structure. Contralateral compensation reactions in the form of hypertrophy and enlargement of the new kidney will occur if the ipsilateral kidney has lost all its functions and has shrinking size (Zelman et al., 1983). Kidney rats that experience hydronephrosis are able to maintain fluid in the vacuole for up to 4 months after total unilateral ureteral obstruction, so that the contralateral reaction will be in the form of new renal hypertrophy afterwards (El-Hakiem et al., 2011).

BUN and Creatinine levels

Statistical analysis result of the BUN level showed that ureteric ligation did not affect the level of BUN between Group I (control), Group II (proximal ureteral ligation), and Group III (distal ureteral ligation) ($p > 0.05$), but the sampling time was influential on the number of BUN ($p < 0.05$). The chart of BUN level showed normal values in Groups I, II, and III in the first week (Figure 7).

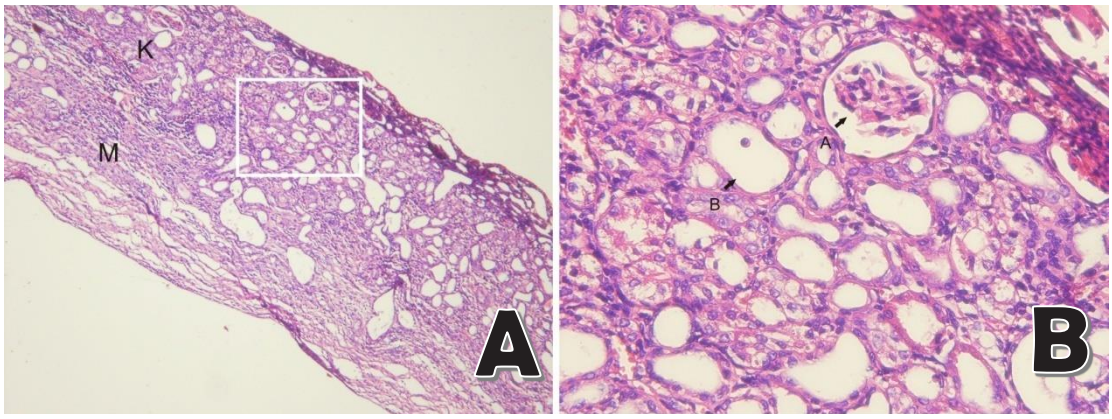

Figure 6. Histopathology of Group II right kidney (proximal right ureteral ligation) 4th week. The kidney parenchyma is thinning, cortex (K), medulla (M), glomerular atrophy (A), tubular dilatation forms multiple cysts (B) (A photo HE stain x 4 objective, B photo HE x 40 objective).

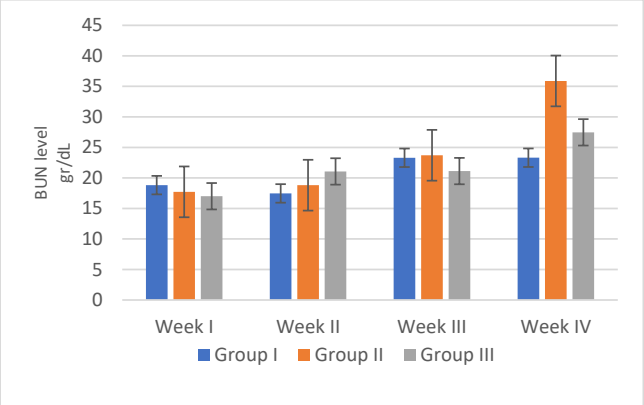

Figure 7. Chart of BUN level 1-4 weeks after ureteral ligation. Group I (control), Group II (proximal ureteral ligation), Group III (distal ureteral ligation).

According to Han et al. (2010), the normal BUN level of 2.5-month-old female Sprague-Dawley rats is 11.7-26.4 mg / dL. The normal condition still lasts until the third week. Entering the 4th week there was an increase in the value of BUN in Group II and Group III. The average Group II BUN at week 4 reached 35.71 mg / dL, while Group III reached 27.47 mg / dL. This number shows the BUN value above normal. The severity of renal function disorders due to obstruction is influenced by the duration of obstruction, location, type of blockage (total / partial), and secondary infections that accompany it (Ito et al., 2004). In the acute phase, the kidneys can still function properly, so patients will not experience azotemia (Kyles, 2005). Renal degenerative changes in the form of congestion and inflammation of the glomeruli begin from the 3rd and 7th day after unilateral ureteral ligation which has an impact on increasing BUN and creatinine (El-Hakiem et al., 2011). The kidneys can still maintain BUN values at normal values until the third week after ligation. BUN Chart (Figure 7) shows an increase in the value of BUN time to time, especially in Groups II and III. The highest increase in the average BUN occurred in Group II (proximal ureteral ligation) at the 4th week. At the early obstruction, the hemodynamic response of renin-angiotensin II will trigger an increase in vascularity towards the kidneys. At that time the GFR will increase so that the urea excretion process can still be maintained in a normal amount (Madsen, 2012). Entering the chronic phase there is a decrease in the amount of active glomerulus accompanied by tubular atrophy and interstitial fibrosis, resulting in decreased filtration function. Ureum can't be filtered properly by the kidneys and carried back into the blood which causes an increase in BUN (El-Hakiem et al., 2011). Rosenfeld and Dial, (2010), state that a BUN escalation will occur if the kidneys have lost 60-70% of the glomerular amount. Thrall et al., (2012), argued that abnormalities of blood profiles would not appear as long as normal nephrons could compensate for damage to other nephrons. When nephron damage reaches 66% the kidneys will lose the function of concentrating urine. If the damage to the nephron has reached 75%, azotemia will appear. The results of the statistical analysis showed that there were significant differences between Group I creatinine (control), Group II (proximal ureteral ligation), and Group III (distal ureteral ligation) ($p < 0.05$). The sampling time from the first week to the 4th week affects the amount of creatinine in the blood ($p < 0.05$).

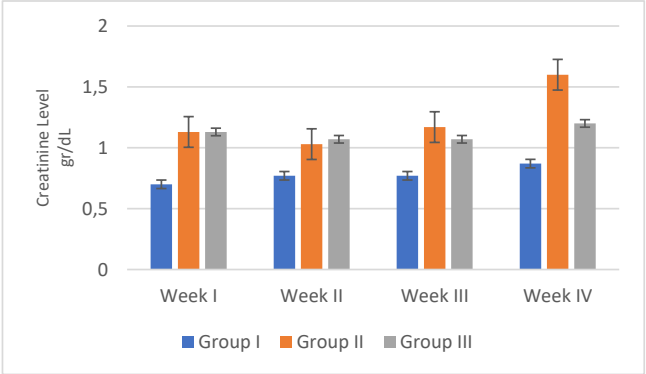

Figure 8. Creatinine chart value 1-4 weeks after ureteral ligation. Group I = control, Group II = proximal ureteral ligation, Group III = distal ureteral ligation.

Figure 8 shows a graph of creatinine escalation in Group II and Group III starting the first week after ureteral ligation. The highest escalation occurred in the 4th week after ligation. This happened in Groups II and III. The highest creatinine level occurred in Group II of the fourth week after ureteral ligation. Castro et al., (2013), stated that normal rat serum creatinine was between 0.02-0.62 mg / dL. Significant escalation in creatinine due to unilateral ureteral obstruction occurs from days 17 and 21 (El-Hakiem et al., 2011). The normal value of creatinine in female Sprague-Dawley rats 2.5 months of age is 0.5 - 0.83 mg / dL (Han et al., 2010).

Creatinine clearance process occurs in glomerulus. It depends on GFR and kidney

condition. When chronic hydronephrosis occurs, the GFR will decrease because urinary back pressure reaches the glomerulus. Creatinine cannot be excreted through urine but re-enters the blood, so serum creatinine will increase (El-Hakiem et al., 2011). In the case of ureteric obstruction, an increase in creatinine occurs rapidly because two types of azotemia occur simultaneously, renal azotemia and post renal azotemia. Renal azotemia occurs when glomerular function begins to decline, whereas post renal azotemia occurs when the urine flow is blocked. Urine will turn towards the kidney so that the non-protein components of nitrogen and toxins re-enter the bloodstream (Rhoades and Tanner, 2003). This study showed that unilateral ureteral ligation in the proximal and distal regions causes an increase in BUN and creatinine and hydronephrosis of the ipsilateral kidney which appears macroscopically and histopathologically. Ipsilateral renal hydronephrosis occurs from the first week after unilateral ureteral ligation, which is characterized by pelvic renal dilatation, parenchymal depletion, vacuoles formation, and fluid deposits in the kidneys. Histopathologically, ipsilateral renal damage characterized by glomerular atrophy, inflammatory response, vacuolization, and fibrosis. Contralateral compensatory response characterized by dilatation of the tubulus convulatus and collecting ducts.

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