Urinary Neutrophil Gelatinase-Associated Lipocalin

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URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN AND CREATININE SERUM BPH PATIENTS WITH ACUTE URINE RETENTION TO DETECT KIDNEY FUNCTION DISORDERS

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ABSTRACT

Objective: *The main objective of this study was to determine renal function in patients with Benign Prostate Hyperplasia (BPH) in acute urinary retention period and two weeks after catheter insertion using creatinine serum and urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) biomarker parameters.* ***Materials & Method:*** *This is an observational co-hort study conducted in patients with BPH with acute urinary retention who came to Soetomo General Hospital, Surabaya. All the patients underwent laboratory investigation that were urinary NGAL and creatinine serum, marker of renal function.* ***Result:*** *The mean creatinine serum of 31 samples when retention phase was 1.6 ± 0.9 mg/dL and it decreased after 2 weeks of urinary catheter insertion (1.46 ± 0.89 mg/dL). Mean urinary NGAL level when retention phase was 308.1 ± 244.8 ng/dL, and after 2 weeks after urinary catheter insertion it decreased to 158.5 ± 123.3 ng/dL. There was significant decreasing creatinine serum and urinary NGAL levels in patients with BPH and acute urinary retention in the retention phase 2 weeks after urinary catheter insertion, with p value < 0.006 and < 0.0001, respectively. There was no significant correlation between the duration of retention and urinary retention volume (p > 0.05).* ***Conclusion:*** *There was a significant decreasing creatinine serum and urinary NGAL levels in patients with BPH and acute urinary retention in retention phase and two weeks after urinary catheter insertion. There was no significant correlation between the urinary NGAL and creatinine serum and the duration of retention and urinary retention volume.*

Keywords: *Neutrophil gelatinase-associated lipocalin, creatinine serum, benign prostate hyperplasia, acute urinary retention.*

ABSTRAK

Tujuan: *Tujuan utama dari penelitian ini adalah mengetahui fungsi ginjal pasien Benign Prostate Hyperplasia (BPH) saat retensi dan dua minggu setelah pemasangan kateter menggunakan parameter serum kreatinin dan biomarker Neutrophil Gelatinase-Associated Lipocalin (NGAL) urine.* ***Bahan & Cara:*** *Studi observasional ko-hort yang dilakukan terhadap sampel pasien BPH dengan retensi urine akut yang datang ke RSUD Dr. Soetomo, Surabaya. Pasien dilakukan pemeriksaan marker gangguan fungsi ginjal NGAL urine dan serum kreatinin saat retensi dan dua minggu setelah pemasangan kateter. Data akan dianalisa secara deskriptif maupun analitik.* ***Hasil:*** *Rerata kreatinin 31 sampel penelitian saat retensi 1.6 ± 0.9 mg/dl dan rerata kadar menurun setelah dua minggu pemasangan kateter 1.46 ± 0.89 mg/dl. Rerata NGAL urine saat retensi 308.1 ± 244.8 ng/dl dan setelah dua minggu pemasangan kateter menurun menjadi 158.5 ± 123.3 ng/dl. Terjadi penurunan signifikan kadar serum kreatinin dan NGAL urine pasien BPH retensi urin akut saat retensi dan setelah dua minggu pemasangan kateter dengan nilai p masing-masing adalah p<0.006 dan p<0.0001. Kadar serum kreatinin dan NGAL urine tidak memiliki hubungan korelasi yang signifikan dengan lama retensi dan volume urine retensi (p>0.05).* ***Simpulan:*** *Terdapat penurunan signifikan kadar serum kreatinin dan NGAL urine pasien BPH dengan retensi urin akut saat retensi dan dua minggu setelah pemasangan kateter. Kadar NGAL urine dan serum kreatinin saat retensi tidak memiliki korelasi yang signifikan dengan lama retensi dan volume urine retensi.*

Kata kunci: *Neutrophil gelatinase-associated lipocalin, serum kreatinin, benign prostate hyperplasia, retensi urine akut.*

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INTRODUCTION

Benign Prostate Hyperplasia (BPH) is a nodular enlargement caused by proliferation of stromal and epithelial prostate gland.[1] The prevalence of BPH increases with age. Sixty percent of men over 50 years old will experience BPH.[1]

Acute urinary retention is one of serious complications on BPH. There are 1.3-8% patients who get acute urinary retention as a consecuence of BPH.[2-5] Acute urinary retention is defined as inability to void spontaneously with lower abdominal pain due to bladder distention.[6-10] The volume or urine in acute urinary retention widely varies.[11]

Bladder outlet obstruction due to BPH results in voiding restriction.[12] The high intravesical pressure will be transmitted in upper urinary tract resulting in high intratubular pressure. This condition will decrease blood flow to kidney and lower glomerular filtration rate (GFR).[13,14] The prevalence of kidney dysfunction in patients with BPH and acute urinary retention widely varied.[15,16]

The gold standard diagnostic tool which is used to evaluate kidney function is inulin and radioisotope clearance. Both of them are not routinely used in acute condition due to impractical, invasive, and not highly available.[17] Nowadays, creatinine level is used as gold standard diagnostic tool to assess renal function.[17,18] Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a novel biomarker for detecting acute renal disorder.[19] Some studies state that NGAL could detect renal destruction early than creatinine serum.[19,20]

NGAL is a low molecule glycoprotein which is produced by human tissue like neutrofil, gaster, lung, colon, trachea, and kidney.[21] NGAL level will increase when there is an injury occurred in glomerular and kidney's tubule. NGAL is filtrated in glomerular, and some of them will be reabsorbed in proximal tubule. Normally, NGAL level is very low. An injury occurs in kidney's tubule will stimulate inflammation process and increased the permeability of its wall. NGAL which is filtrated in glomerular should be reabsorbed in proximal tubule, but because of the injury, this process will be disrupted, and results in high NGAL level in urine.[22-24]

The principle management of BPH with acute urinary retention is bladder decompression by introducing urinary catheter.[25,26] After urinary catheter insertion, a trial without of catheter (TWOC) could be considered a few weeks later.[25] Renal function improvement after obstruction release could be divided into two phase; tubular phase (0-2 weeks); glomerular phase (2 weeks-3 months). Some of the improvements will be coming after two weeks and continue till the 3rd week.[14]

OBJECTIVE

This study is done to evaluate renal function in BPH with acute urinary retention in acute condition and two weeks after urinary catheter insertion. In this study, renal function of each patient is evaluated using creatinine level and urinary NGAL parameter.

MATERIAL & METHOD

This was an observational study co-hort. The samples were all patients with BPH and acute urinary retention who came to Soetomo General Hospital during research period of time and eligible for inclusion criteria. This research is done from April until September 2015.

The inclusion criteria were men 50 years old or older with acute urinary retention (pain and urinary volume 400 ml or greater) due to BPH who agreed to attend this research. Patient will be excluded from this research if he got heavy infection, had history of urinary retention or urinary catheter insertion in the last one month, prostate surgery, liver and pulmonary disorder.

All samples who were eligible for the inclusion criteria underwent clinical and laboratory investigation including urinary NGAL, creatinine serum, PSA, complete blood test, urinalysis, urine culture, and clinical chemistry. Patients also will undergo radiological investigation such as abdominal plain photo, trans-abdominal and trans-rectal USG. Urinary NGAL, creatinine serum, urinalysis, urine culture, ureum, and complete blood test will be check serially, when acute retention and 2 weeks after urinary catheter insertion. The kidney also will be evaluated using USG 2 weeks after urinary catheter insertion.

All the laboratory materials will be processed in the Clinical Pathology Laboratory Soetomo General Hospital. All the urine samples will be centrifuged with 3000 rpm for 15 minutes before it will be stored in refrigerator (-80°C). Urinary NGAL is checked using NGAL kit DCLN20 type from R & D Inc. and read by ELISA using 450 nm wave length.

The results will be displayed in distribution table. The correlation between creatinine level and urinary NGAL when retention period with duration and urine volume of retention will be analysed using Program SPSS 22. T-test between creatinine and urinary NGAL when acute retention and 2 weeks after urinary catheter also will be analysed using the same program.

RESULTS

There were 31 samples who fulfilled the inclusion criteria. From the demographic analysis, the youngest age was 53 years old, the oldest age was 88 years old with mean 67.4 ± 7.2. Table 1 showed the mean duration of acute urinary retention was 567.7 ± 498 minutes (9.5 hours) with mean pain score was 5 ± 1.59. Mean urinary retention volume was 737 ± 286 ml. Mean prostate volume 48.2 ± 13.8 ml. Mean PSA level was 5.6 ± 1.7 ng/dL.

Mean creatinine level when acute urinary retention period was 1.6 ± 0.9 mg/dL, and decreased 2 weeks after urinary catheter insertion (mean 1.46 ± 0.89 mg/dL). The mean ureum level when acute urinary retention period was 17.7 ± 9 mg/dL and became 16.1 ± 8 md/dL 2 weeks after urinary catheter insertion. The mean GFR of all the samples when acute urinary retention period was 47.7 ± 19.4 ml/minute, and got better 2 weeks after urinary catheter insertion (51.4 ± 20.1 ml/minute).

Urinary NGAL level when acute urinary retention period was 308.1 ± 244.8 ng/dL. This level decreased 2 weeks after urinary catheter insertion (158.5 ± 123.3 ngdL).

The mean difference creatinin was 0.1 ± 0.17. While GFR mean difference was 3.7 ± 10.1. Urinary NGAL difference was 139.9 ± 222.2.

Sixteen out of 31 samples (51.6%) had comorbid disease like hypertension, diabetes mellitus, and/or hypertension and diabetes mellitus. Twenty out of 31 samples (64.5%) had a positive urine culture, and increased to be 21 patients (67.7%) 2 weeks after urinary catheter insertion.

Table 2 shows results of kidney evaluation using USG whan acute urinary retention period. There were 7 patients (22.6%) who experienced

Table 1. Patient Characteristics.

	Minimum	Maximum	Mean	Standard Deviation
Age (year)	53	88	67.4	7.2
Duration of retention (minute)	120	2880	567.7	498
VAS	2	8	5	1.59164
Body Weight (kg)	45	90	61.8	9.2
Height (cm)	150	172	163.2	5
Prostate Volume (ml)	30	86.9	48.2	13.8
PSA (ng/dl)	0.8	8.7	5.6	1.7
GFR during retention (ml/minute)	8.6	101.4	47.7	19.4
GFR after two weeks (ml/minute)	8.6	99.3	51.4	20.1
Delta GFR (ml/minute)	-24.3	36.1	3.7	10.1
Urinary retention volume (ml)	500	2000	737	286
Urinary production (ml)	1500	2500	1887	234.9
Bun during retention (mg/dl)	6	44	17.7	9
Bun after two weeks (mg/dl)	8	42	16.1	8
Creatinine during retention (mg/dl)	0.8	5	1.6	0.9
Creatinine after two weeks (mg/dl)	0.7	5	1.46	0.89
Delta creatinine (mg/dl)	-0.3	0.5	0.1	0.177
Urinary NGAL during retention (ng/ml)	56	930	308.1	244.8
Urinary NGAL after two weeks (ng/ml)	11	620	158.5	123.3
Delta urinary NGAL (ng/dl)	-53	830	139.9	222.22

Table 2. Patient characteristics based on co-morbidity, urine culture, and ultrasonography result.

	Positive (%)	Negative (%)	Total
Co-morbidity	16 (51.6)	15 (48.4)	31 (100)
Urine culture			
During retention	20 (64.5)	11 (35.5)	31 (100)
After two weeks	21 (67.7)	10 (32.3)	31 (100)
Hydronephosis			
During retention	7 (22.6)	24 (77.4)	31 (100)
After two weeks	6 *(19.4)	25 (80.6)	31 (100)

*hydronephrosis decrease

Table 3. Creatinine and urinary NGAL differences.

Variable	During retention	After 2 weeks Evaluation	Delta	P value
Creatinine	1.56 ± 0.9	1.46 ± 0.89	-0.1 ± 0.17	0.006
Urinary NGAL	308.1 ± 244.8	158.5 ± 123.3	-139.9 ± 222.2	<0.0001

Table 4. Creatinine and urinary NGAL correlation with duration of retention and urinary retention volume.

During retention	Duration of retention		Urinary retention volume	
	p	r	p	r
Creatinine	0.514	-0.122	0.841	-0.038
Urinary NGAL	0.367	-0.168	0.97	-0.303

Spearman's rho test, $p < 0.05$

hydronephrosis and the remaining patients (77.4%) were without hydronephrosis. After 2 weeks of urinary catheter insertion, 1 patient became normal (no hydronephrosis), while the others still had hydronephrosis, but with a slight improvement.

There was a significant difference in creatinine serum level in patients with BPH and acute urinary retention in acute phase and 2 weeks after urinary catheter insertion, with p value = 0.006 (table 3).

Urinary NGAL level in patients with BPH and acute urinary retention in acute phase decreased significantly after 2 weeks after urinary catheter insertion (p value < 0.0001).

The correlation between creatinine serum level and urinary NGAL when acute urinary retention period with the retention duration and urinary retention volume was analyzed using Spearman's correlation test. Creatinine level and urinary NGAL when acute urinary retention period does not have a significant correlation with duration of retention and urinary volume retention 9 (table 4).

DISCUSSION

The mean age of the 31 samples was 67.4 years old. This was similar to other literature stated that the olger the age, the higher the possibility of experiencing acute urinary retention. Patients with 70 years old have 4-6 times to get that condition compared with them aged less than 40 years old.[15] Mustonen found that the mean age of patient with acute urinary retention was 69 years old.[16]

The mean duration of urinary retention was 568 minutes or 92 hours. That was a little bit different with other literatures. The mean duration of Mustonen's research was approximately 31 hours.[17] This could be caused by social, cultural, and also geographical difference of each patient. The mean urine volume in this research was 737 ml. That was similar to other researches which stated that the range of urine volume in patients with acute urinary retention was 500-1000 ml.[6]

Mean creatinine level during retention 1.6 mg/dl and after two weeks evaluation decrease to

1.46 mg/dl. Creatinine serum decreasing cause of obstruction relieve by catheterization. There was significant different creatinine level during retention and two weeks after catheterized p = 0.006. Mustonen had same result but he conduct renal function follow up until 6 month.[16] Tubular recovery began at first two weeks after relieve obstruction. After two weeks glomerular recovery was began and continue until at least for three month.[14]

Mean GFR patient during retention 47.7 ml/minute and after two weeks 51.4 ml/minute. Acute urinary retention can cause obstruction and increase renal pressure. This condition made GFR decrease during retention. Soon after releasing obstruction GFR gradually improved. This GFR changes was significant with p = 0.049. Mustonen also found significant improvement clearance creatinine patient after one month and 6 month evaluation $p<0.05$.[16]

NGAL expression in urine increase more than 100 times normally during injury.[17] Mean NGAL level during retention in this study 308 ng/dl and after two weeks mean NGAL level 158.5 ng/dl. NGAL urine during retention and two weeks after evaluation had significant differences $p<0.0001$. It showed that urethral catheter for relieve obstruction can improved NGAL level.

Creatinine and NGAL urine not significant correlated with duration of retention and urinary retention volume. This result different from literature that mention prolong obstruction can cause severe tubular damage and influence their renal function.[13]

Level NGAL and creatinine increasing in few patients although had catheterized. It seem, they renal function decrease cause of different factors. This study had several limitations. First, this study used creatinine not inulin clearance or renogram as gold standard for renal function test compare with NGAL urine. Second, we had not analyzed confounding factor such as co-morbidity, drugs consumption, diet modification, and fluid intake, which it can influence renal function. Need further investigation considering those confounding factors, larger number of patients, serial marker evaluation and longer follow up for renal function.

CONCLUSION

BPH patient who have acute urinary retention had significant decreasing of creatinine and urinary NGAL levels during acute urinary retention and two weeks after catheterized. Level creatinine and NGAL urine during retention not significant correlate with prolong duration of retention and urinary retention volume.

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