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Sensitivity and Specificity of Urine N-Acetyl-β-D-Glucosaminidase as an Early Biomarker For Acute Kidney Injury

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Abstract

Background
The estimated incidence of Acute Kidney Injury (AKI) is two to three cases per 1,000 patients. Seven percent of hospitalized patients and about two-thirds of patients in intensive care units develop acute kidney injury and the mortality rates range between 25 and 80 percent. Disruption in epithelial brush border of proximal tubular cell causes N-Acetyl-β-D-Glucosaminidase (NAG) to be released to the urine and the amount of enzyme could be directly correlated with tubular disruption.The aims of this research is to determine the sensitivity and specificity of NAG urine examination as an early biomarker for acute kidney injury.

Methods
There's 66 subjects who met the inclusion criteria. All the subject were checked for the NAG urine level with Cloud Clone kit and creatinine serum were also checked 48 hours after admission.

Results
The results showed in the cut-off point of 7.98 Ng/mL, urine NAG has a sensitivity of 68.6% and specificity 77.4%, positive predictive value 77.42%, negative predictive value 68.57 % and accuracy of 72.73%

Conclusions
The result shows that urine NAG examination is more sensitive and specific as an early biomarker for Acute Kidney Injury compared to creatinine serum.

Key words : Acute Kidney Injury, N-Acetyl-β-D-Glucosaminidase , sensitivity, spesificity

Background

The estimated incidence of Acute Kidney Injury (AKI) is 2: 3 cases per 1000 patients. Two-thirds of patients treated in intensive care suffer from AKI and the mortality rate reaches 25-80%. NAG is a lysosomal enzyme in the proximal tubule of the kidney. NAG will increase in

exposure to nephrotoxic drugs, chronic glomerular disease, and diabetes nephropathy and is also sensitive to detecting AKI in patients in intensive care, which is indicated by raising serum creatinine in 12 hours. Disorders of the epithelial of the proximal tubule will cause NAG to exit into the urine and the amount detected is directly related to tubular disorders.[1-3]

Several new biomarkers are being studied in various groups of patients to find biomarkers that are more specific, sensitive, and able to detect kidney injury than creatinine which is still considered the gold standard that has been used for decades to detect acute and chronic kidney injury. In this case, for example, the urine NGAL biomarker is a low molecular weight urine protein that will be found in the urine if there is a disruption of renal tubular reabsorption due to damage to renal tubular epithelial cells. However, urine NGAL can also increase in systemic stress without AKI. This causes NGAL to be less specific as biomarkers of AKI. Urine itself is a product of the kidneys that can be obtained easily compared to taking serum or plasma samples, and is suitable for serial measurements. Urine contains enzymes and proteins released from injured tubular cells and is able to become the initial marker of the origin of injured tissue.[4-6]

NAG is a lysosome enzyme that is most commonly found in the proximal tubular epithelial cells of the kidneys which serves to catalyze the terminal glucose hydrosis process into glycoproteins. NAG has a molecular weight of 140 kDa and cannot be absorbed or secreted by the kidney tubules. Under normal circumstances, enzymes with a molecular weight of more than 70 kDa cannot be filtered by the glomerulus to then enter the urine. Thus, if NAG has a molecular weight of 140 kDa capable of being detected in the urine, it can be the initial marker of damage to the renal proximal tubule cells due to leakage of urine NAG from proximal renal tubular epithelial cells to the proximal tubular lumen of the kidney.[7-10]

This enzyme has been proven to be more specific and sensitive to renal tubular injury than creatinine and other marker biomarkers when combined, for example, NGAL and Kim-1. NAG is stable in urine, and variations between individuals are minimal.[11-13] Urine samples are adequate for practical testing using the ELISA method with high reproducibility. Increased NAG levels in urine can be detected within 12 hours after damage to the proximal renal tubule, with levels reaching a peak on the second day and disappearing on the fourth day.

Methods

This diagnostic test was carried out in the ICU, HCU and P1 General Hospital Dr. Mohammad Hoesin Palembang in June 2018 until August 2018. A total of 66 samples were obtained that met the inclusion criteria. All samples were examined for urine NAG levels using a Cloud Clone kit and serum creatinine values were examined 48 hours after the patient admitted. The results of the study will be analyzed using the Receiver Operating Characteristic (ROC) curve with SPSS® version 25.00 and MedCalc version 18.6.

Results

This diagnostic test had been carried out in the ICU, HCU, and P1 rooms at general hospital Dr. Mohammad Hoesin Palembang started from June 2018 until August 2018 with the aim of knowing the value of sensitivity and specificity of urine NAG examination compared with serum creatinine examination.

The study sample was all patients who had just been treated in the ICU, HCU and P1 who met the inclusion and exclusion criteria. There's 66 samples that met the inclusion and exclusion criteria were the subjects in this study. There is no sample that withdraws or drops out during the course of the study until the study finished.

From the results of the study it was found that from 66 samples, 39 (59.1%) of them were male and 27 (40.9%) were female. The average age was 50.32 ± 16.591 with a median age of 50 years. The average age of the male subjects was 52.62 ± 17.75 with a median age of 58 years. The average age of female subjects was 47 ± 14.43 and the median age was 49 years.

Most of the samples were diagnosed with hemorrhagic Cerebro Vascular Disease (CVD) with 15 people (22.7%) followed by obstetrics cases, Intracranial space occupying lesion and post digestive Surgery with 8 subjects (12.1%) each.

There's 30 subjects (45.5%) were diagnosed with Non-AKI, and 36 subjects (54.5%) had AKI where 22 subjects with a diagnosis of AKI stage 1 (33.3%), subjects with of AKI stage 2 in 6 subjects (9.1%) and subjects with a diagnosis of AKI stage 3 as many as 8 subjects (12.1%).

From 66 study samples, 14 samples (21.2%) were found to have positive values both from the results of urine NAG and serum creatinine, and 24 samples (36.4%) had negative values from both examinations.

Diagnostic test results in the form of sensitivity, specificity, accuracy, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, likelihood ratio test, AUC (Area Under Curve), and reliability test. Analysis of urine NAG examination results with standard creatinine gold using the ROC curve with SPSS version 25.0 software (IBM Corporation and others, NY, USA) and MedCalc version 18.6 (MedCalc Software, Mariakerke, Belgium).

The sensitivity value in this study was 68.6% and the specificity in this study was 77.42% which meant that the NAG level of urine could specifically describe the diagnosis of AKI but was less sensitive.

Table 1. Diagnostic Value of NAG Urine Examination

No	Diagnostic Value	Value	95% CI
1	Sensitivitas (Sn)	68.57%	31.38% - 66.01%
2	Spesifisitas (Sp)	77.42%	66.27% - 94.55%
3	Accuracy	77.73%	52.42% – 76.47%
4	Positif predictive value (PPV)	77.42%	1.26 – 7.20
5	Negative predictive value (NPV)	68.57%	0.43 – 0.88
6	Prevalence	53.03%	40.34% - 65.44%
7	Likelihood ratio positive (LR+)	3.04	1.26 – 7.20
8	Likelihood ratio negative (LR-)	0.41	0.43 – 0.88
9	Area under curve (AUC)	0.753	-
10	Reliability Test	0.63	-

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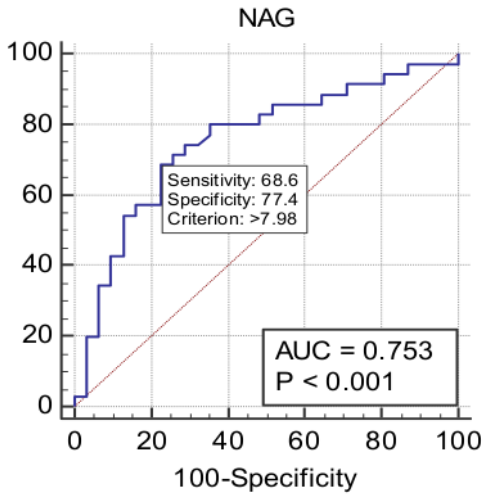

Picture 1. ROC curve of NAG Urine

Discussion

From this study the characteristics of heterogeneous research subjects were obtained. Research subjects who entered the ICU and HCU, as well as P1 were caused by a variety of cases in both medical, surgical, obstetrics and neurologic cases. The average age of 66 samples is 50 years. The average age of the male study sample was 53 years. The average age of the female study sample was 47 years. From the results of the study it was found that from 66 samples, 39 (59.1%) of them were male and 27 (40.9%) were female.

This result is slightly different from the Hoste 2015 study which also found that the average age of AKI sufferers was 63 years of age with 64.4% of men. Whereas in Santos's 2015 study, it was found that the average age of suffering from AKI was 42.5 ± 20.7 with the number of men 66.3%.

From 66 samples, 30 subjects (45.5%) were diagnosed with Non-AKI. And found 36 subjects (54.5%) with a diagnosis of AKI where as many as 22 subjects with AKI stage 1 (33.3% of the total patients, and 61.1% of the AKI group), subjects with a diagnosis of AKI stage 2 were

6 subjects (9.1% of the total all patients, and 16.67% of the AKI group) and subjects with a diagnosis of AKI stage 3 were 8 subjects (12.1% of the total patients, and 22.2% of the AKI group).

The incidence of AKI in this study approached the results of the Hoste study in 2015 in which the incidence of AKI was found to be 57.3%, and in the Santos study in 2015, the incidence of AKI was slightly different, namely 32.9%. This difference in numbers is probably due to the different number of samples, as well as the characteristics of the population of the study sample. The incidence of AKI stage 1 in this study is close to the results of Bellomo's research in 2017 which states that 50% of AKI patients treated in intensive care experience AKI stage 1. Santos's study in 2015 resulted in 33.7% of patients experiencing AKI stage 1, 29.4% experiencing AKI stage 2, and 36.9% experienced AKI stage 3.

In this study, the most patients were diagnosed with Carebro Vascular Disease Hemorrhagic, with 15 samples (22.7%), followed by 8 intracranial SOL patients (12.1%) and 8 digestive (12.1%) digestive patients.

Based on bivariate analysis of diagnostic values of urine AKI and NAG, from 66 study samples 24 samples (36.36%) were found had positive values both from the results of urine NAG and serum creatinine levels and as many as 24 samples (36.36%) which had negative values from both examinations. A total of 7 subjects (10.60%) showed false positives, and 11 subjects (16.67%) who showed false negatives. In this study also found that urine NAG had a 7.98 Ng / mL cut-off point, sensitivity 68.57% and specificity 77.42%, with odds ratio of 7.4805 (95% CI 2.4808 - 22.5562). This odds ratio shows that when urine NAG is obtained > 7.98 Ng / mL the possibility of diagnosing AKI is 7,4805 times greater.

Using a receiver operating characteristic (ROC) curve can be found in area under curve (AUC) of urine NAG of 0.753. The AUC value can be used to measure the accuracy of the diagnostic test in general with the limitations of the AUC value of 0 to 1. The AUC value that is closer to 1 indicates that the diagnostic test is good. The AUC interpretation criteria are as follows: > 50-60% (very weak), > 60-70% (weak), > 70-80% (moderate), > 80-90% (good), > 90-100% (good) very good). It was concluded that urine NAG levels in this study had moderate accuracy (75%).

When compared with other study, It showed a very high AUC value of 1.0 (95% CI: 0.98-1.00) in a study that assessed urine NAG activity in AKI patients compared with non-AKI patients.

Han's 2008 study of urine NAG showed an AUC value of 0.97 (95% CI: 0.91-1.00). The study showed that urine NAG has a value of AUC 0.845 with a 8.3 U / mmol cut-off point, with a sensitivity of 100% and specificity 81%, positive predictive value 50% and negative predictive value 100%. [14-18]

Conclusion

The incidence of AKI in critically ill patients treated in the ICU, HCU and P1 geneal hospital of Dr. Mohammad Hoesin Palembang is 54.5%. Urine NAG at cut-off point levels > 7.89 Ng / mL is 68.57% sensitivity, 77.42% specificity, 77.42% positive predictive value, 69.57% negative predictive value, with odds ratio 7.4805, accuracy 72.73% and reliability test 0.6.

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