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Original Article

Results of proteinuria measurement using semiquantitative dipstick in children with fever or nephrotic syndrome

Chatidjah Alaydrus, Yati Soenarto, M.P. Damanik

Abstract

Background Proteinuria is a major determinant of the progression of renal disease. Quantitative measurement of proteinuria within a 24-hour period of urine collection was the accepted method of evaluation, but is tedious and prone to error in the absence of a reliable collection. We evaluated the diagnostic value of AUTION Sticks 10 TA to diagnose proteinuria in children with fever and nephrotic syndrome.

Methods This study was conducted at the pediatric ward of Sardjito Hospital. Proteinuria levels were measured using semiquantitative dipstick methods with AUTION Sticks 10 TA using a 24-hour urine sample collected at the first examination until the following day. Proteinuria level was also measured by Esbach method as gold standard.

Results A total of 120 children aged 16 years old were recruited. In the fever group, AUTION Sticks 10 TA couldn't be used for the diagnostic test. AUTION Sticks 10 TA +2 to diagnose intermediate proteinuria produced a sensitivity of 60%, a specificity of 89%, a positive predictive value of 43% , a negative predictive value of 94%, a positive likelihood ratio of 5.4, a negative likelihood ratio of 0.45. To diagnose nephrotic proteinuria, AUTION Sticks 10 TA +3/+4 produced a sensitivity of 90%, a specificity of 91%, a positive predictive value of 96%, a negative predictive value of 77%, a positive likelihood ratio of 10, a negative likelihood ratio of 0.11.

Conclusion AUTION Sticks 10 TA +2 is sufficiently accurate for a diagnostic test of intermediate proteinuria (Esbach value) while +3/+4 is sufficiently accurate for a diagnostic test of nephrotic proteinuria (Esbach value) in children. In the fever group, dipstick result can not explain the Esbach value. **[Paediatr Indones 2008;48:10-14]**.

Keywords: *diagnostic test, AUTION Stick 10 TA, proteinuria*

Proteinuria is the excretion of protein urine within 24 hours above 150 mg (10-20 mg/dL).[1] Proteinuria can be identified as either a transient or a persistent finding and can represent a benign condition or a serious disease.[2] The range of proteinuria is variable, but the upper limit of normal protein excretion in a healthy child is 150mg/24 hours. The prevalence of proteinuria in American children was 1-10%.[3,4] Proteinuria in excess of 150 mg/24 hours may or may not reflect pathologic conditions.[5-7] In patients with nephrotic syndrome, the quantity of protein excretion in the urine may illustrate the disease activity.[6] The severity of proteinuria found in a population study may be used to predict the outcome. Proteinuria +1 does not increase the risk of end stage renal disease, while proteinuria +2, +3 and+4 increase the risk by 7.6, 16.1 and 19.5 times, respectively.[8]

Proteinuria can be estimated quantitatively or qualitatively. The quantitative examination may be

From The Department of Child Health, Medical School, Gadjah Mada University, Yogyakarta, Indonesia.

Reprint requests to: Chatidjah Alaydrus, MD, Department of Child Health, Medical School, Gajdah Mada University, Jl. Kesehatan No. 1, Sekip Utara, Yogyakarta 55281, Indonesia. Tel. 62-274-587333. Fax. 62-274-583745.

performed either by measuring the protein excretion in a 24 hour time period with an Esbach method or by quantifying the protein: creatinine ratio in a fresh urine sample. This is a well-accepted method, however, it is difficult to use in infants and children, it is time-consuming, impractical and prone to error associated with improper urine collection.[6] Qualitative measurement using a dipstick, on the other hand, is highly subjective, and may give biased result in the presence of other substances in the urine. [2,9-11]

Semiquantitative measurement of proteinuria with dipstick is getting popular since this test is sensitive for albumin, rapid and easy to perform, does not take 24 hours and not influenced by subjectivity of the examiner since the result will be read by a semiautomatic reader. The semiquantitative dipstick which is utilized in Sardjito Hospital is the AUTION Stick 10 TA with the analyzer PocketChem^{TM} UA Compact Urine Analyzer. The result of the proteinuria test is read within 2 seconds and is interpreted to be negative when the protein level in the urine is <10 mg/dL, ± / trace (10-20 mg/dL), positive/+ 1 (21-30 mg/dL), + 2 (31-100 mg/dL), +3 (101-600 mg/dL) and +4 (601-1000 mg/dL).[12] The proteinuria test using a semiquantitative dipstick has a sensitivity of 70-86%, a specificity of 68-100%, a positive predictive value of 89% and a negative predictive value of 60%.[13,14] The aim of study was to determine the diagnostic value of AUTION Sticks 10 TA to detect proteinuria in children with fever and nephrotic syndrome.

Methods

This study was done at in-patient ward of the Pediatric Department in Sardjito Hospital, Yogyakarta from July 1st 2005 to March 31st 2006. This was an observational study using a diagnostic test. The inclusion criteria were all patients with fever, nephrotic syndrome (new patients and those with relapse) admitted to Sardjito Hospital between July 2005-March 2006 and consented to be included in the study and signed an informed consent form. The exclusion criteria were patients who were using a catheter, undergoing radiologic examinations with contrast (IVP) and gross hematuria, pH urine<3, BJ>1030. The study sample was recruited consecutively. Approxi-mately 5 cc of urine was taken from midstream urine to perform the dipstick test using AUTION Sticks 10 TA. Parents or caretakers of patients were asked to collect all urine excreted for 24 hours which elapse a from the first examination to the following day. If the patient was admitted at night, the urine was collected from 8.00 am the following morning until 8.00 am the next day. Both dipstick examination using AUTION Sticks 10 TA and Esbach were performed in the Clinical Pathology Laboratory of Sardjito Hospital. Data of this study was analyzed using Epi Info 6 for DOS and Cat Maker.

Children who were admitted to the in-patient ward of the Pediatric Department from July 1st 2005 – March 31st 2006 who met inclusion criteria were included in this study.

Results

There were 120 children used as subjects for the study. The baseline characteristics of subjects are presented in **Table 1**.

In the fever group, there were no trace or +2 to +4 walves which could be classified into b and d cells, therefore the cell was valued 0. Consequently, the diagnostic test couldn't be performed. Analysis with the t test for children with fever showed that there was no statistically significant difference between 0 and +1 in the dipstick results to detect proteinuria.

Among the children with fever, there was no result of dipstick >+1, therefore the t tested for 2 independent samples between +1 and +2.

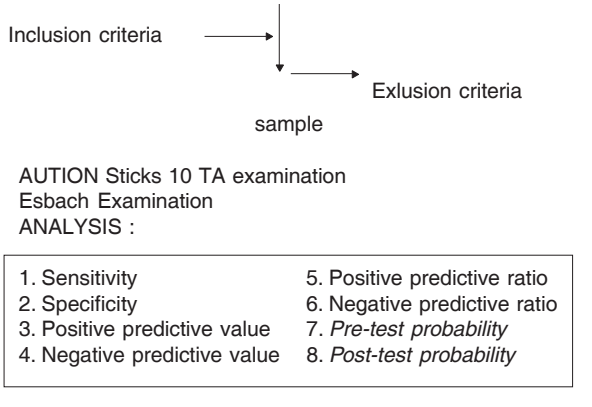

Figure 1. Scheme of study procedure and analysis

Table 1. Baseline characteristics of study subjects of the proteinuria diagnostic test study in children

Variable	Number of Subjects (Percentage %)				
	-/trace	+1	+2	+3	+4
Age					
1- 5 years	19 (15.8)	11 (9.2)	1 (0.8)	2 (1.6)	6 (5)
6 -11 years	33 (27.5)	15 (12.5)	5 (4.2)	7 (5.8)	4 (3.3)
12 – 18 years	4 (3.3)	3 (2.5)	2 (1.6)	2 (1.6)	6 (5)
Sex					
Boys	38 (31.6)	18 (15)	6 (5)	8 (6.7)	9 (7.5)
Girls	18 (15)	11 (9.2)	2 (1.6)	3 (2.5)	7 (5.8)
Diagnosis					
1. UTI	18 (15)	3 (2.5)	0	0	0
2. Non UTI	38 (31.6)	20 (16.6)	0	0	0
3. New Nephrotic syndrome	0	0	0	3 (2.5)	2 (1.6)
4. Relaps/old Nephrotic syndrome	0	6 (5)	8 (6.7)	8 (6.7)	14(11.7)

Table 3 shows the accuracy of the AUTION Sticks 10 TA to detect intermediate proteinuria (4-40 mg/ m^2/ hour). The highest Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Values are obtained on AUTION Sticks 10 TA with +2. The highest Positive Predictive Ratio was also obtained using AUTION Sticks 10 TA +2 which was as high as 5.4 using the normogram Bayes theorem with a prevalence of intermediate proteinuria in this study (12%). Thus, the post test probability value was 42%.

Table 4 shows the accuracy of AUTION Sticks 10 TA in detecting nephrotic proteinuria (>40 mg/ m^2/hour). The highest Sensitivity, Specificity, Positive Predictive and Negative Predictive Values are obtained on AUTION Sticks 10 TA using +3/+4. The highest Positive Predictive Ratio was also obtained on AUTION Sticks 10 TA +3/+4 which was as high as 10. This value, when estimated using the normogram Bayes theorem with a prevalence of nephrotic proteinuria in this study of 73%, the post test probability value will be 96%.

Subjects with nephrotic syndrome participated in this study showed a dipstick result of +1 to +4, thus we performed the t test for 2 independent sample between +1 and +2, +1 and +3, +1 and +4, +2 and +3, +2 and +4 as well as +3 and +4. Table 5 demonstrates a statistically significant result between all groups. **Table 6** shows a significant difference between the dipstick results of +2 and +3 or +4 to detect proteinuria in children with nephrotic syndrome, while **Table 7** illustrates that there is no statistically significant result between dipstick result of +3 dan +4 to detect proteinuria in children with nephrotic syndrome.

Table 2. Result of the t test for dipstick with result of 0 and +1 for children with fever

	Mean Esbach	t	SD	P	df
0	0.000	1.933	0.035	0.057	77
+1	0.014		0.000		

Discussion

The analysis of the diagnostic test included sensitivity, specificity, the predictive value and the ratio of a test

Table 3. Diagnostic values of AUTION Sticks 10 TA to detect Esbach result of Esbach 4-40 mg/m^2/hour*

	+1 Value	CI 95%	+2 Value	CI 95%	+3/+4 Value	CI 95%
Sensitivity (%)	20	15-55	60	17-100	20	15-55
Speciificty (%)	86	75-97	89	79-99	25	11-39
PPV (%)	17	13-46	43	6-80	4	3-20
NPV (%)	89	78-99	94	86-100	69	44-94
LRP	1.1	0.21-9.95	5.4	1.68-17.38	0.27	0.05-1.55
LRN	0.93	0.59-1.47	0.45	0.15-1.32	3.2	1.56-6.55

*Abbreviations. PPV = positive predictive value; NPV = negative predicitive value; LRP = likelihood ratio of the positive result; LRN = likelihood ratio of the negative result

Table 4. Diagnosti values of AUTION Sticks 10 TA to detect Esbach result >4-40 mg/m²/hour in the SN Group

	+1 Value	CI 95%	+2 Value	CI 95%	+3/+4 Value	CI 95%
Sensitivity (%)	3	-3- 10	7	-2-16	90	79-100
Specificity (%)	55	25-84	55	25-84	91	74-100
PPV (%)	17	-13-46	29	-5-62	96	90-100
NPV (%)	17	5-30	18	5-30	77	54-100
LRP	0.07	0.01-0.56	0.15	0.03-0.65	10	6.8-26.5
LRN	1.77	1.03-3.05	1.71	0.99-2.96	0.11	0.04-0.33

* See Table 3 for abbreviations.

Tabel 5. Result of the t test to compare proteinuria between all groups of dipstick +1 with +2, +3, +4 in SN group

	Mean (Esbach)	t	*P*
+1	2.729	-	-
+2	3.217	1.306	0.03
+3	3.657	-1.810	0.026
+4	5.442	-1.95	0.021

Table 6. Result of the t test to compare proteinuria between all groups with a dipstick result of +2, +3, +4 in the SN group

	Mean (Esbach)	t	*P*
+2	2.729	-	-
+3	3.657	-1.289	0.04
+4	5.442	-1.695	0.01

Tabel 7. Result of the t test to compare proteinuria in all groups with a dipstick result of +3, and +4 in the SN group

	Mean	t	SD	*P*
+3	3.657	-1.406	2.929	0.172
+4	5.443		3.742	

against a gold standard. The result of this study showed that in children with fever, there was no result of Esbach >4 mg/m²/hour. Analysis with the t test showed that there was no statistically significant difference between a dipstick result of 0 and +1 to detect proteinuria in children with fever, therefore it may be concluded that the dipstick result may not reflect Esbach in children with fever.

The accuracy of AUTION Sticks 10 TA +2 to detect intermediate proteinuria in children with nephrotic syndrome showed a sensitivity of 60%, a specificity of 89% and a PPV of 43%. Agarwall *et al*[6] reported a specificity of 98%, however, there was no result for sensitivity due to empty cell a. The result of AUTION Sticks 10 TA +3/+4 to detect nephrotic proteinuria showed a sensitivity of 90% (CI 95% 74;99) which means that the test has an ability of 90% to detect proteinuria in group with nephrotic proteinuria and only 10% of nephrotic proteinuria cases that were not detected due to false negative results. In this case, the dipstick showed a specificity of 91%, which means that the test has an ability of 91% to determine that nephrotic proteinuria is not present and only 9% of nephrotic proteinuria cases are falsely detected due to a false positive result.

The study by Agarwal *et al*[6] showed a comparable sensitivity and specificity, 80% and 100%, respectively. The negative predictive value was high, 96%, which means that if the result is negative, the probability that the child doesn't have proteinuria is 96%. The study in Sardjito Hospital was comparable to that of Agarwal *et al*[6], with an NPV of 77% and a very high PPV of 96%. In Agarwal[6] study, there was no dipstick for of +3/+4 with Esbach <40 mg/m²/hour, that resulted in an empty cell. The study by Abitbol *et al*[13], 1990 obtained PPV of 89%, which may be interpreted that if the dipstick (+), 89% patient had proteinuria.

The predictive value is influenced by disease prevalence, sensitivity and specificity. The higher the prevalence, the lower the predictive value. This study was performed in a referral hospital, where the prevalence was higher than in the common population. If this test was performed in the community, the predictive value would be higher.[15] The result of this study showed that the utilization of AUTION Sticks 10 TA + 2 will increase the probability of correct diagnosis of intermediate proteinuria by 5.4 times, while +3/+4 will increase the probability of correct diagnosis of nephrotic proteinuria by 10 times compared to the use of the previous methods of diagnosis.

The disadvantage of using AUTION Sticks 10 TA in this study was the inability to differentiate between proteinuria in prerenal, renal or postrenal proteinuria. Rupprecht[16] stated that the urine dipstick was not able to detect light chain

immunoglobulin such as Bence Jones protein. The differentiation between glomerular and tubular is made using α1 microglobulin, α2 macroglobulin and imunoglobulin (Ig G). Stojimirovic and Petrovick[17] indicated that the analysis of proteinuria type should be done with protein α1 microglobulin, α2 macroglobulin and Ig G as well as the measurement of total protein in the urine. The result of AUTION Stick 10 TA +2 was accurate in diagnosing intermediate proteinuria (Esbach), while +3/+4 was accurate in diagnosing nephrotic proteinuria (Esbach) in children with nephrotic syndrome in Sardjito Hospital. For children with fever, the result of the dipstick may not reflect the Esbach. Based on these study results, AUTION Sticks 10 TA can be used for early diagnosis of proteinuria in children with nephrotic syndrome, while in children with fever, further study is needed.

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