Utility of Urinalysis in Discriminating Cardioembolic Stroke Mechanism

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Objective: To determine whether elevated urine erythrocyte (red blood cell) and leukocyte (white blood cell) counts, reflecting concomitant renal and cerebral emboli of cardiac origin, would be useful in discriminating cardioembolic (CE) from non-CE stroke in acute ischemic stroke.

Design: Consecutive patients presenting within 24 hours of ischemic stroke over 3 3/4 years were studied. Patient medical history and urinalysis data, including white blood cell count, red blood cell count, specific gravity, and glucose and protein levels at admission, were analyzed and compared with the final determination of stroke subtype. Multivariate analysis (CE vs non-CE stroke) was performed using a classification and regression tree that included all 5 urine variables as potential predictors. Additional predictors entered into the classification and regression tree model were age, presence of urinary tract infection at admission, history of hypertension, history of diabetes mellitus, and serum creatinine level.

Results: A total of 341 individuals met the study criteria. Their mean age was 68.6 years; 49.8% were female, 70.9% were white, and 38.7% had the CE stroke subtype. In bivariate analysis, age ($P=.009$), urine white blood cell count ($P=.02$), urine red blood cell count ($P=.005$), urine specific gravity ($P=.02$), and serum creatinine level ($P=.02$) were significantly higher in those with the CE vs the non-CE stroke subtype. In the classification and regression tree, 58.3% of those with CE stroke were correctly classified and 84.7% of those with non-CE stroke were correctly classified, for an overall accuracy of 71.5%. The best single predictor for the CE stroke subtype was a white blood cell count of greater than 14.5/µL, followed by a red blood cell count of greater than 41.7/µL and a serum creatinine level greater than 1.08 mg/dL (95.5 μmol/L). Based on the distribution in the first 2 divisions in the tree, a patient could be placed into 1 of 4 categories that corresponded to 3 levels of CE stroke likelihood: low (25%), moderate (50%), and high (80%).

Conclusion: Urinalysis may have utility in the early identification of the CE stroke subtype in patients with acute ischemic stroke.

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Ischemic stroke is a heterogeneous condition that has been classified into subtypes based on mechanism of infarction. Stroke subtyping has important clinical implications with regard to treatment and clinical prognosis. For instance, the cardioembolic (CE) stroke subtype generally carries a poorer prognosis than the small-vessel subtype, and often requires warfarin as opposed to antiplatelet treatment for secondary stroke prevention. Discriminating stroke subtype reliably is a critical element of ischemic stroke diagnosis. However, distinguishing stroke subtype is sometimes not straightforward, and identifying additional diagnostic tools, particularly cheap and widely available tests, is desirable.

Routine urinalysis (UA) is frequently performed during hospitalization for ischemic stroke, to identify evidence of urinary tract infection. However, we are unaware of any previous studies that have evaluated the role of UA in distinguishing stroke subtype. One possible connection between stroke subtype and UA data would be the presence of elevated urine red blood cell (RBC) and white blood cell (WBC) counts due to renal infarction from concomitant renal and cerebral emboli of cardiac origin. Renal infarction is generally underrecognized, but it has been shown that up to 71% of patients experiencing atrial fibrillation (the most common condition producing CE stroke) exhibit urinary indexes of renal infarction, such as increased WBC and RBC counts.

In this study, we hypothesized that urine containing elevated levels of RBCs and WBCs would be useful in discriminating CE from non-CE stroke in acute ischemic stroke.
Methods

We analyzed demographic, clinical, and UA data collected prospectively on consecutive patients older than 18 years admitted with acute ischemic stroke at a university medical center from September 1, 2002, through June 5, 2006. Ischemic stroke was defined as a measurable neurologic deficit (confirmed with radiography) present for longer than 24 hours due to a presumed ischemic cause. Stroke typing was performed per the modified Trial of Org 10172 in Acute Stroke Treatment criteria. Patients who experienced a transient ischemic attack were excluded. Patients were also excluded from the study if the UA result was obtained longer than 24 hours from stroke onset, if they had an “undetermined” stroke subtype, if they had a creatinine level greater than 1.6 mg/dL (>141.4 µmol/L) (to eliminate moderate to severe renal insufficiency as a possible cause of irregular UA results), or if they received intravenous or intra-arterial thrombolysis. The investigators were unaware of the goals of this study at patient examination and UA evaluation.

Five urine variables were preselected based on a literature review suggesting possible clinical and biological relatedness to stroke subtype: urine-specific gravity, urine WBC count, urine RBC count, urine glucose level, and urine protein level. Urine protein and glucose levels were recorded as negative, trace, 1+, 2+, 3+, and 4+. These were coded on a 0 to 5 scale to make them ordinal variables. We also identified evidence of urinary tract infection as a possible reason for abnormal UA results. The results of patients whose initial urine culture grew bacteria (<24 hours after stroke) were recorded as positive for urinary tract infection.

Wilcoxon rank sum and Fisher exact tests were used to compare demographic and clinical variables for CE and non-CE stroke. Because the data were highly skewed to “0” for protein and glucose levels and RBC and WBC counts, a classification and regression tree (CART) was used to determine potentially clinically useful thresholds in multivariate analysis. A CART considers all of the given predictors of a specific outcome and makes a binary split using 1 predictor at the level that yields the largest difference in the percentage for this outcome. Then, within each branch of the initial dichotomization, it searches additional variables for additional binary splits that improve classification. This model was chosen because it can handle highly skewed data, create normal limits for a unique scenario, and contribute to a clinically useful algorithm of patient classification. The CART was set to predict the outcome of CE vs non-CE stroke, and it incorporated the already mentioned 5 potential urine predictors and 5 additional predictors that could potentially influence long-term renal function/urine results: age at stroke, serum creatinine level, history of hypertension, history of diabetes mellitus, and presence of urinary tract infection within 24 hours of admission. To avoid classification bias, we did not include well-known CE stroke risk factors, such as atrial fibrillation and coronary artery disease, in the CART model, because it is likely that investigators already used this information in classifying stroke subtype within our study.

Of 791 consecutive patients who experienced an ischemic event, 341 (43.1%) met the study criteria. Reasons for exclusion were as follows: 245 had UA results obtained beyond 24 hours from stroke onset, 126 had a final diagnosis of transient ischemic attack, 100 had a stroke of undetermined cause, 52 had a creatinine level of greater than 1.6 mg/dL (>141.4 µmol/L), and 38 received intravenous or intra-arterial thrombolysis (some patients had >1 reason for exclusion). By only using urine collected during the initial 24 hours in the hospital, we hoped to eliminate abnormal UA results due to hospital-acquired infections. Among patients meeting the study criteria, 38.7% (132 of 341) had a CE stroke. Twenty-four patients were receiving warfarin treatment before the index stroke, with an admission internationalized ratio mean of 1.38 and a median of 1.45.

In bivariate analysis, age, female sex, history of coronary artery disease, history of atrial fibrillation, serum creatinine level, urine WBC count, urine RBC count, urine specific gravity, and greater stroke severity were significantly associated with CE stroke (Table). The CART analysis selected 5 hierarchical predictor steps for CE vs non-CE stroke (Figure). The first predic-
A creatinine level of 1.08 mg/dL or less. In the classification of stroke, as opposed to 26.3% (55 of 209) of those with a creatinine level above this threshold had a CE stroke, compared with 46.2% (18 of 39) with a threshold of 41.7/µL.

The second predictor used for those with a high urine WBC count was urine RBC count, with a threshold of 41.7/µL. In those patients with a WBC count of greater than 14.5/µL, 63.0% (46 of 73) had a CE stroke, compared with 32.1% (18 of 39) with a threshold of 41.7/µL.

In the tree, a patient can be placed into 1 of 4 categories that correspond to 3 levels of CE stroke likelihood: low (25%), moderate (50%), and high (80%). Based on the distribution in the first 2 divisions in the tree, a patient can be placed into 1 of 4 categories that correspond to 3 levels of CE stroke likelihood: low (25%), moderate (50%), and high (80%).

Our study suggests that UA has some utility in distinguishing CE from non-CE stroke in those experiencing an acute ischemic stroke. We found that urine WBC
count was the most important urinary variable for making this distinction and, along with urine RBC count, tended to be significantly higher in those with CE vs non-CE stroke. Our results are in accord with the few studies that have looked at the urinary variables in patients experiencing atrial fibrillation. The preeminence of WBC count as a predictor is likely because of the inflammatory response initiated by the acute renal infarct. Our finding of higher creatinine levels in those experiencing a CE stroke may also be further evidence of a greater likelihood of renal infarctions in those with CE stroke. Conceivably, the acute renal infarct may have caused a slight impairment in overall kidney function, manifested by the mildly elevated creatinine level we noted in our study. However, this assertion cannot be made with certainty because we did not have information on premorbid creatinine levels.

The CART analysis underscored the results of the bivariate analysis and reinforced the potential role of urine data in placing patients experiencing an ischemic stroke into categories of differing probabilities for CE stroke. Urine WBC and RBC count variables were selected for the first 2 tiers of the classification algorithm. The selection of age as a latter classification variable likely reflects its correlation with increased risk of atrial fibrillation.

The results of our study should be interpreted with caution because of the limited sample size and the retrospective analytic nature. We did not use renal isotope scans to confirm renal infarctions, nor did we collect urinary and serum lactate dehydrogenase levels, which may be elevated in those with renal infarction. However, given the difficulty in precisely determining stroke subtype, and the widely available and inexpensive nature of UA, the finding of a substantial potential contribution of UA to CE stroke classification warrants confirmatory studies in independent populations.

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