Original Article

The Accuracy of Leukocyte Esterase and Glucose Levels in Synovial Fluid for Diagnosis of Acute Septic Arthritis: A Preliminary Report

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Objective: To evaluate the diagnostic performance of synovial leukocyte esterase and glucose in differentiating between acute bacterial arthritis and inflammatory arthritis.

Materials and Methods: A cross-sectional study was conducted from November 2015 to August 2016. Patients older than 18 years who had painful or swollen joints and who were suspected of having joint infection were enrolled. Synovial fluid aspirated from the affected joint was centrifuged to precipitate RBC and clear supernatant was obtained. Leukocyte esterase and glucose were identified using a standard colorimetric urine strip test which was graded as negative, 1+, 2+ or 3+. Statistical analysis was done using STATA 13.0.

Results: There were 21 patients suspected of having septic arthritis. The average age was 68.5±14.5 years, and 52.4% were female. The incidence of septic arthritis was 33.3%. Leukocyte esterase has a diagnostic sensitivity of 100% and a specificity of 64.3%. The synovial glucose test has a sensitivity of 71.4% and a specificity of 71.4%. A combination of positive (2+ or 3+) leukocyte esterase and negative synovial glucose yielded a sensitivity of 71.4%, specificity of 92.9%, likelihood ratio [LR] of a positive test of 10.0, LR of a negative test 0.31, and area under receiver operative characteristic [ROC] curve 0.82.

Conclusion: Combined synovial leukocyte esterase and glucose can be a useful diagnostic test for septic arthritis.

Keywords: Leukocyte esterase, Glucose, Septic arthritis, Diagnosis, Accuracy

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Septic arthritis is an important musculoskeletal problem. Delayed diagnosis has been associated with high mortality rates of up to 15% in a normal host and up to 56% in an immunocompromised host[1]. The present gold standard for diagnosis of septic arthritis is synovial culture with 75 to 90% sensitivity, although the culturing process takes at least 24 hours. Gram stain is commonly used to obtain results within an hour, but its sensitivity limit is between 29 to 50%[2].

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In septic arthritis, neutrophils in synovial fluid release leukocyte esterase enzyme and consume glucose resulting in a low serum glucose level. A laboratory test involving dipping a treated strip (dipstick) into synovial fluid can easily detect the presence of the enzyme. Ester hydrolysis and the azo-coupling reaction mechanism changes the color of the urine dipstickto purple (azo dye)[3].

From a review of the literature, we found that enzyme leukocyte esterase has a diagnostic limitation: it cannot differentiate a joint with septic arthritis from inflammatory joint[2]. A study that combined a leukocyte esterase and a glucose test reported a sensitivity for septic arthritis as high as 94.7% and a specificity of 73.2%[3,4]. However, the inclusion

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criteria for diagnosis of septic arthritis were not clearly defined[4]. In addition, the diversity of the study population may have brought out the differences in the diagnostic ability of the urine strip test.

For this reason, we proposed to study the accuracy of leukocyte esterase and glucose for diagnosis of septic arthritis. This test is also inexpensive, rapid, and easy to do, so it could be useful for differentiating between septic arthritis and other inflammatory conditions. An objective of this study was to evaluate the diagnostic performance of synovial leukocyte esterase and glucose in differentiating septic arthritis from inflammatory joint.

Materials and Methods

A cross-sectional study was conducted at Ramathibodi Hospital from 2015 to 2016. The study was approved by the Ramathibodi Ethics Committee. We included patients aged older than 18 years who had joint pain, swelling and limited range of motion [ROM] within the previous 6 weeks. We excluded patients who were not willing to participate in the study, who had used antibiotics in the past 6 weeks, or who had undergone arthroplasty. Baseline characteristics of participants including age, gender, joint involvement, body temperature, and presence of fever (body temperature >37.8 celsius) were collected.

We obtained synovial fluid from the joint which was suspected as septic arthritis. Synovial fluid was aspirated with an 18-gauge needle. A meticulous aspiration technique was used to minimize blood contamination in the synovial fluid as that would interfere with the leukocyte esterase test. The synovial fluid samples were divided into three portions for cell count, cell culture, and urine strip testing for leukocyte esterase and glucose. Cell count was performed on the first portion to quantify the number of leukocytes as well as polymorphonuclear cells [PMN]. The second portion of each of the three synovial fluid samples was sent to a laboratory immediately for bacterial culture. The third portion of the aspirated synovial fluid which was to be used with the test strips was centrifuged at 4,000 revolutions per minute to obtain supernatant. One drop of synovial fluid was applied to a standard chemical test strip to detect the presence of leukocyte esterase and glucose. After 60 to 120 seconds, the urine test strip was analyzed with a Cobus U 411 urine analyzer (Roche Diagnostics Limited, Switzerland). Analysis of each sample was repeated to ensure the reliability of the test.

The gold standard for diagnosis of septic arthritis is based on the results of synovial fluid culture, gram staining[1,2] and clinical response to antibiotics[2]. Synovial fluid cultures and gram stains were verified by technicians and approved by an experienced clinical pathologist [MK]. A positive culture or gram stain was considered evidence of the presence of septic arthritis. In cases of a negative synovial culture and gram stain, clinical response to antibiotics was used for diagnosing septic arthritis. Arthritis clinical response was evaluated using the ACR 50 response following American College of Rheumatology response criteria[6] which are based on a 50% improvement in the number of swollen and tender joints, including three additional parameters of pain and physical function, acute phase reactant erythrocytese dimentation rate [ESR] and c-reactive protein [CRP] levels, patient assessment of global status, and disease activity. Clinical response was documented by an experienced rheumatologist [PC]. Patients who had a negative synovial culture, a negative gram stain, and did not meet ACR 50 criteria were diagnosed as aseptic arthritis.

Statistical analysis

The calculated sample size for our study was 80. The alpha error was 0.05 with a power of 0.8. The accuracy of the test was 80%. Sample size estimation was based on a model used in a previous study[4]. Continuous variables are presented as mean and standard deviation and categorical data are presented as percentage. Comparison between two means was performed using the unpaired Student's t-test. We calculated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy, likelihood ratio of positive test, likelihood ratio of negative test, area under the receiver operating characteristic [ROC] curve for the leukocyte esterase strip test, the glucose strip test, and the two-test combination in diagnosing septic arthritis. All statistical analysis was performed using STATA 13.0 (StataCorp, College Station, Texas, USA).

Results

Twenty-nine patients were initially determined to be eligible for the study. Of those, six patients were excluded due to previous antibiotic administration and two patients were excluded who had prolonged synovitis lasting more than 6 hours. Twenty-one patients were finally included in the present study.

Baseline characteristics of the patients are shown in Table 1. Average age was 68 years and most of the participants were female. The most common joint

involvement was the knee. Fourteen patients (67%) had underlying diseases. The incidence of septic arthritis was 33%, and 23% of patients presented with fever. Six out of seven synovial fluid samples from patients with clinical septic arthritis had positive cultures. The pathogens isolated were *Streptococcus agalactiae* species (two patients), *Streptococcus agalactiae* (Streptococcus group B) (two patients), *Streptococcus dysgalactiae* (one patient) and *Staphylococcus aureus* (one patient). One patient diagnosed with septic arthritis had a clinical response to antibiotics without identification of the organism (ACR 50 increased more than 50%). All the septic arthritis patients underwent arthrocentesis. Treatments included antibiotic administration (one patient), arthrotomy with debridement and antibiotic administration (five patients), and arthroscopic debridement and antibiotic administration (one patient).

Table 1. Baseline characteristics of study patients

Baseline characteristics	n = 21
Mean age (SD)	68.52 (14.49)
Gender, n (%)	
Male	10 (47.62)
Female	11 (52.38)
Joint, n (%)	
Knee	18 (85.71)
Elbow	2 (9.52)
Shoulder	1 (4.76)
Underlying diseases (%)	
None	7 (33.33)
Cardiovascular disease	4 (19.05)
Endocrine	3 (14.29)
Seronegative disease	2 (9.52)
Gout	1 (4.76)
Kidney	1 (4.76)
Malignancy	2 (9.52)
Central nervous system	1 (4.76)
Septic arthritis (%)	7 (33.33)
Body temperature >37.8 Celsius (%)	10 (47)
Fever with septic arthritis (%)	5 (23.8)

For the 14 patients diagnosed as having aseptic joints, the final diagnosis was 11 aseptic arthritis, one gouty arthritis, one reactive arthritis, and one seronegative arthritis. All patients were treated with non-steroidal anti-inflammatory drugs; the patient with gouty arthritis was additionally prescribed colchicine.

Both the synovial fluid leukocyte count and percentage of PMNs were higher in the septic fluid samples (Table 2). Mean leukocyte count was more than 100,000 cells/mm^3 in the septic group, and approximately 50,000 cells/mm^3 in the aseptic group. PMNs were significantly higher in the septic group (94%) compared to the aseptic group (78%) with a *p*-value of 0.0185. The results of the semi-quantitative leukocyte esterase test were consistent with the elevation in the synovial fluid leukocyte count and the percentage of PMNs as shown in Table 3. Leukocyte counts were more than 100,000 cells/mm^3 and PMNs were higher than 90% in leukocyte esterase ++ or +++ results. Samples with negative or + leukocyte esterase had approximately 29,000 cells/mm^3, and PMNs were 72%.

Distribution of urine strip test results in septic and aseptic arthritis are shown in Table 4. For each individual synovial fluid sample, the two urine strips consistently had the same reading (-, +, ++ or +++) for leukocyte esterase, and (-, +, ++, +++, ++++) for glucose. The combined tests with a positive (++ or +++) leukocyte esterase strip test reading and a negative glucose strip test clearly improved the specificity and positive predictive value for diagnosing septic arthritis when compared with single test to 92.9%, and 83.3%, respectively. However, sensitivity dropped slightly from 100% to 71.4% (Table 5).

Discussion

In our study, the urine dipstick test for leukocyte esterase alone had 100% sensitivity and 64.3% specificity. Glucose alone had 71.4% sensitivity and 71.4% specificity. The combined synovial leukocyte esterase and glucose had 71.4% sensitivity and 92.9% specificity. The results show the combined

Table 2. Synovial fluid cell count

Cell count	Septic (n = 7)	Aseptic (n = 14)	*p*-value
Leukocyte (cell/mm^3), mean (SD)	118,422.9 (115,600)	51,369.6 (43,455.3)	0.1824
PMN%, mean (SD)	94.4 (38)	77.9 (22.7)	0.0185

PMN = [*polymorphonuclear] cells

Table 3. Synovial fluid characteristics from the urine strip test

Test	LE – or + (n = 9)	LE ++ (n = 3)	LE +++ (n = 9)
Leukocytes (cell/mm^3)	29,234.89	355,960	124,126.7
PMN (%), mean (SD)	71.9 (25.8)	92.3 (3.1)	91.9 (9.0)
Septic sample (%)			
GLU –	0	0	5 (83.3)
GLU +	0	0	1 (16.7)
GLU ++	0	0	0
GLU +++	0	1 (100)	0 (0)
Aseptic sample (%)			
GLU –	3 (33.3)	0	6 (66.7)
GLU +	4 (44.4)	1 (33.3)	2 (22.2)
GLU ++	1 (11.1)	0	0
GLU +++	0	2 (66.7)	0 (0)

LE = leukocyte esterase; PMN = polymorphonuclear cells; Glu = glucose

Table 4. Distribution of strip test results between septic and aseptic arthritis

Test results	Septic arthritis (n = 7)	Aseptic arthritis (n = 14)
LE++ or +++ (%)		
Yes	7 (100)	5 (35.7)
No	0 (0)	9 (64.3)
GLU- (%)		
Yes	5 (71.4)	4 (28.6)
No	2 (28.6)	10 (71.4)
LE++ or +++ (%) and Glu-		
Yes	5 (71.4)	1 (7.1)
No	2 (28.6)	13 (92.9)

LE = leukocyte esterase; Glu = glucose

leukocyte esterase and glucose had significantly improved specificity while retaining acceptable sensitivity. In most of the cases diagnosed as septic arthritis, pathogens were detected by synovial culture. Only one case used ACR 50 criteria for diagnosis of septic arthritis.

Our study demonstrates that urine strip testing for leukocyte esterase and glucose has a high accuracy for diagnosis of septic arthritis. Positive leukocyte esterase and glucose have an excellent positive predictive value of 83.8% and a likelihood ratio of a positive test of 10. Results of our study are similar to previous studies[7,8], but the sensitivity and specificity are lower in the previous studies due to inadequate sample size, different inclusion criteria, different criteria for diagnosis of septic arthritis, and use of an earlier version of urine dipstick. Our gold standard for diagnosing septic arthritis is based on previous studies[1,2]. It is composed of synovial fluid culture, synovial fluid gram staining, and clinical response to antibiotics. These criteria may not applicable to all studies or in all clinical settings. We tried to increase sensitivity to detect septic arthritis and to lower false negative results by adding synovial fluid gram stain as a parallel test to synovial fluid culture. We also used the clinical response to antibiotics established by American College of Rheumatology that which has been widely accepted all over the world to accommodate the diagnostic capability in cases of negative results of synovial fluid culture and gram stain. In this study, six out of seven patients were diagnosed with septic arthritis based on positive synovial fluid cultures. The other patient was diagnosed with septic arthritis based on clinical response to antibiotics. None of the seven patients had a positive synovial fluid gram stain.

Table 5. Diagnostic value of the strip test for septic arthritis

Diagnostic value	Test mean (95% confidence interval)		
	LE++ or +++	GLU -	LE ++ or +++ and GLU -
Sensitivity (%)	100 (59 to 100)	71.4 (29.0 to 96.3)	71.4 (29.0 to 96.3)
Specificity (%)	64.3 (35.1 to 87.2)	71.4 (41.9 to 91.6)	92.9 (66.1 to 99.8)
PPV (%)	58.3 (27.7 to 84.8)	55.6 (21.2 to 86.3)	83.3 (35.9 to 99.6)
NPV (%)	100 (66.4 to 100)	88.3 (51.6 to 97.9)	86.7 (59.5 to 98.3)
Accuracy (%)	76.2 (53.8 to 91.8)	71.4 (47.8 to 88.7)	85.7 (63.7 to 97.0)
LR of positive test	2.8 (1.39 to 5.65)	2.5 (0.97 to 6.47)	10.00 (1.43 to 70.0)
LR of negative test	0	0.4 (0.12 to 1.35)	0.31 (0.09 to 1.00)
ROC area	0.82 (0.69 to 0.95)	0.71(0.50 to 0.93)	0.82 (0.63 to 1.00)

PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio; ROC = receiver operating characteristic

In a retrospective study[7] which included 57 patients suspected of periprosthetic joint infection, the patients routine test for antibiotic cement, or idiopathic painful joint replacement who underwent joint aspiration. The criteria for diagnosis of peri-prosthetic infection were based on leukocyte and PMNs counts that were lower than those of septic arthritis. Another prospective study, which included 146 suspected septic arthritis participants[8], used pathogens isolated from typical sources of septic arthritis other than synovial fluid and turbid synovial fluid without crystals as criteria for diagnosis. The criteria in these two studies may result in an increase in false positives leading to an over-estimation of the incidence of septic arthritis, high sensitivity, and negative predictive value. Although our study and these previous two studies used urine dipsticks from the Roche Company, the dipsticks were from different generations various e.g., Chemstrip 10 UA, Chemstrip 7[7], Combur 9[8] rather than the Cobus U 411 used in our study. The differences in the version of urine dipsticks may have affected leukocyte esterase detection and diagnostic ability in both sensitivity and specificity.

Strengths of the present study are a well-designed methodology with clearly defined inclusion and exclusion criteria, use of the best available urine strip test in a quaternary care hospital, using standard ACR 50 for diagnosis of septic arthritis in cases of negative synovial culture, and appropriate statistical analysis and diagnostic values. Limitations of our study include inadequate sample size leading to a negative amount of synovial glucose and limited internal validity. Since this is only a preliminary study, results should be applied with careful consideration, especially as relates to the diagnostic ability of leukocyte esterase and glucose levels. An extension of the current study or additional studies are needed to determine the true diagnostic properties of these tests. In addition, the results may be limited to a single quaternary-care hospital which may have different epidemic causative agents than in a general hospital. However, as the clinical symptoms and pathogens identified in our study are common in Thailand, the results may be appropriate for some clinical applications.

In the future, if it is possible to detect more accurately measure enzyme leukocyte esterase and glucose levels, a better cutoff point of leukocyte esterase and glucose may become available, allowing more precise diagnosis of septic arthritis. An improved system could potentially differentiate between septic and inflammatory joints with greater accuracy.

Our study found that the urine strip test for leukocyte esterase and glucose was suitable for diagnosing septic arthritis. This test is simple, rapid, and inexpensive. In practice, synovial fluid should be centrifuged before testing to reduce blood component contamination.

Conclusion

The combination of leukocyte esterase and glucose strip tests has the potential to serve as a simple and helpful tool, allowing prompt and accurate diagnosis of septic arthritis. It can be used to screen for septic arthritis in emergency situations. The combination strip test may be more valuable for ruling in than ruling out septic arthritis.

What is already known on this topic?

A combination of a leukocyte esterase and a glucose urine strip test documented high sensitivity

and moderate specificity for diagnosing septic arthritis. However, unclear diagnostic criteria for septic arthritis limited clinical application.

What this study adds?

With definite inclusion and exclusion criteria, the positive leukocyte esterase and the negative glucose urine strip test provided 71.4% sensitivity, 92.9% specificity, and 85.7% accuracy. The combined test is suitable for ruling in septic arthritis.

Potential conflicts of interest

The authors declare no conflict of interest.

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