

Efficiency of Rapid Antigen Test in Diagnosis of Acute Streptococcal Tonsillopharyngitis

Tarik Acar¹, Birsen Ertekin¹, Abdullah Sadik Girisgin², Esmâ Ozturk¹, Serpil Bilgi³

¹ Beyhekim State Hospital, Emergency Department, Konya, Turkey.

² Necmettin Erbakan University, Meram Faculty of Medicine, Department of Emergency, Konya, Turkey.

³ Beyhekim State Hospital, Microbiology Department, Konya, Turkey.

Correspondence Author: Tarik Acar

E-mail: drtarikacar@gmail.com

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ABSTRACT

Objective: Group A beta hemolytic streptococcus (GABHS) is the most common bacterial cause of acute tonsillopharyngitis. Cases with bacterial infection suspicion should undergo rapid antigen test (RAT) and/or throat culture test in addition to clinical criteria, since it may lead to serious complications.

Method: A total of 220 adult and pediatric patients admitted to the emergency department between April-May 2016 with complaints of fever and sore throat, and diagnosed as acute tonsillopharyngitis were prospectively enrolled to the study. All participants had Centor score ≥ 2 and they underwent RAT. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of RAT results of both groups were compared. Throat culture was considered as gold standard method.

Results: Mean age of the study population was 22,5 \pm 16,9 (1-72) years. 57% (n=61) of the pediatric group, and 42.5% (n=48) of adult group were male. Sensitivity of RAT in adults and pediatric group was 62% vs. 57%, and specificity of the test was 96% vs. 97%, PPV was 55% vs. 80%, and NPV was 97% vs. 93%, respectively.

Conclusion: We found low sensitivity and PPV values of RAT. Also, low levels of sensitivity decrease the possibility of RAT to be a diagnostic tool for the diagnosis of GABHS.

Keywords: Pharyngitis, streptococci, emergency care, rapid antigen test, culture

1. INTRODUCTION

Acute tonsillopharyngitis is a benign and self-limiting disease characterized with sore throat and difficulty in swallowing. It is the cause of 1-2% of total outpatient clinic administrations in United States which makes 12 million patients (1). These applications cause needless antibiotic prescriptions (2). Most of tonsillopharyngitis cases are viral in origin however; bacterial etiology must be excluded because of its serious complications (3). The most common cause of bacterial tonsillopharyngitis is Group A beta hemolytic Streptococcus (GABHS). Certain diagnosis and rapid onset of antibiotherapy is crucial since it may lead to serious complications such as acute rheumatic fever and acute glomerulonephritis (4).

Clinicians should consider rapid antigen test (RAT) and/or throat culture test in addition to clinical diagnostic criteria in patients with bacterial infection suspicion while establishing streptococcal tonsillopharyngitis diagnosis (5). Thus, a number of scoring system criteria were developed to help identifying bacterial agent. Modified Centor Criteria is most commonly used one. Throat culture positivity rate is 56% in patients with 4 criteria, whereas that probability is 2.5% in patients with 0 criteria for the diagnosis of GABHS (6).

But sensitivity (12%-92%) and specificity (30%-93%) of this criterion are reported variously (7).

Although culture is the gold standard diagnostic test for streptococcal pharyngitis this takes 2 days for the isolation of the microorganism. Sensitivity of culture in GABHS identification is reported as 90-95% (8). Nevertheless, laboratory requirements, cost, and duration of throat culture limits its use as a diagnostic tool in low-income or developing countries. On the other hand, RAT is a diagnostic test with high sensitivity and specificity which gives result within minutes (9). Rapid antigen test enables early initiation of treatment and subsequently symptomatic relief within 48 hours. Furthermore, this precludes spreading of the microorganism and needless prescription of antibiotics (10).

Rapid antigen test has been used in Europe and United States for a long time; however, it is not commonly used in our country, especially in the emergency departments yet. Thus, in this study we aimed to investigate diagnostic value of RAT for GABHS on patients admitted to emergency department with acute tonsillopharyngitis according to Centor classification, its relation with throat culture results, and its effect on antibiotic prescription rate.

2. METHODS

A total of 220 adult and pediatric patients admitted to the emergency department of a state hospital with fever and sore throat complaints between April-May 2016 and diagnosed with acute tonsillopharyngitis were prospectively enrolled to the study. Demographic data, complaints, physical examination findings and vital signs of the participants were recorded. All patients applying Centor criteria which includes $38 \geq$ fever by history, tonsillar exudates, tender anterior cervical adenopathy, age and absence of cough, acute rhinorrhea were divided into two: above (adults) and below (pediatric) 18 years of age. All participants had ≥ 2 score according to Centor classification. Exclusion criteria were as follows: antibiotic usage in last 2 weeks, patients with a history of acute rheumatic fever or acute glomerulonephritis. Patients with Centor score 0-1 were discharged after symptomatic treatment and recommendations. Rapid antigen test was applied to the ones with Centor score ≥ 2 . Two study groups (adults vs. pediatric group) were compared in terms of sensitivity, specificity, PPV and NPV of their RAT results. Throat culture test was accepted as gold standard method. Furthermore, the clinicians were asked about their antibiotic prescription decision after physical examination before they noticed the RAT results. Both groups were compared in terms of RAT results and the clinician's decision on antibiotic prescription. The present study was compatible with ethical rules of Helsinki Declaration. All participants or their parents signed informed consent form. Local ethics committee of Necmettin Erbakan University, Meram Faculty of Medicine approved the study protocol (date: 2017, number: 872).

2.1. Microbiologic Method

Two throat swabs were carefully (avoiding to touch tongue, uvula, or elsewhere) collected from oropharynx of each patient by an experienced doctor who evaluated and examined the patient. The first collected swab was exposed to RAT which is an immunochromatographic test used to qualitatively detect StrepA antigen (Turklab Strep A Test/İzmir/Turkey). Second swabs were taken into Stuart agar which contains sheep blood (BioMerieux/İstanbul/Turkey) seeded and then incubated for 24 hours. Catalase test was performed on the reproducing and beta hemolysis making colonies while culture plates were evaluated. Catalase-negative ones were exposed to PYR (L-pyronidin beta naphthylamide). PYR (+) colonies were taken into passage and loaded into automated antibiogram and identification device (Vitek[®]2; Healthcare/bioMerieux/USA). The bacterial strains identified as *Streptococcus pyogenes* were reported as 'GABHS (Strep. pyogenes) reproduction'. Other identified strains were reported as 'normal oral flora reproduction' (11, 12).

2.2. PYR Method

PYR-impregnated papers were immersed to distilled water and inseminated with beta hemolysis catalase-negative

bacteria which degrade L-pyronidin beta naphthylamide by the naphthylamidase enzyme. Then indicator is added 2 minutes later. Pink color indicated the presence of PYR. Enterococci, *S.pyogenes* and *Staphylococcus lugdunensis* are also PYR-positive. Thus, if the detected colonies are catalase-negative and PYR-positive, they are identified as *S. pyogenes* by the automated bacteria identification (13).

2.3. Statistical Analysis

All data was analyzed with SPSS 21.0 software (IBM Turk Limited Company /Istanbul/Turkey). All variables were summarized by descriptive variables. Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed. Continuous variables were listed as mean \pm standard deviation, and categorical variables were listed as percentages (%). Chi-square test was used to compare categorical variables of independent groups. McNemar test was used for comparison of categorical variables of 2 dependent groups. Sensitivity, specificity, PPV, and NPV of RAT results of both groups were calculated. Statistical significance was defined as $p \leq 0.05$.

3. RESULTS

Mean age (minimum-maximum) of the study population (n=220) was 22.5 ± 16.9 (1-72) years. Mean age of the pediatric group (n=107) was 7.9 ± 4.3 years, and that of adult group (n=113) was 36.3 ± 12.2 years. Fifty-seven percent (n=61) of the pediatric group, and 42.5% (n=48) of the adults were male. The antibiotic prescription rate of the clinicians who had examined the patient and unannounced about the RAT (-) and throat culture (-) results of the patient was 54.2% (n=58) in pediatric group, and 43.3% (n=49) among adult group (107 of 220 (48.6%) patients in total). Pediatric and adult groups were comparable in terms of RAT results ($p=0.450$) and throat culture results ($p=0.104$). There was a statistically significant difference between study groups in antibiotic prescription decision rates on the basis of clinical findings ($p=0.005$) (Table 1 and 2). Rapid antigen test sensitivity was 62% vs. 57%, specificity was 96% vs. 97%, PPV was 55% vs. 80%, and NPV was 97% vs. 93% in adult vs. pediatric group, respectively. Table 3 and 4 demonstrates false-positive and false-negative RAT results of RAT in adult and pediatric groups, respectively.

Table 1. Decision to prescribe antibiotics in childhood

| | | Culture | | Total |
|---------------------|--------------------------|----------|----------|-------|
| | | Positive | Negative | |
| Decision of doctors | Antibiotic Writing | 14 | 61 | 75 |
| | Antibiotic isn't Writing | 0 | 32 | 32 |
| Total | | 14 | 93 | 107 |

Sensitivity:100%; Specificity:34%; PPV:18%; NPV:100% ; Consistency: 42%

Table 2. Decision to prescribe antibiotics in adults

| | | Culture | | Total |
|---------------------|--------------------------|----------|----------|-------|
| | | Positive | Negative | |
| Decision of doctors | Antibiotic Writing | 8 | 51 | 59 |
| | Antibiotic isn't Writing | 0 | 54 | 54 |
| Total | | 8 | 105 | 113 |

Sensitivity:88%; Specificity:51%; PPV:13%; NPV:100% ; Consistency: 54%

Table 3. RAT results in childhood

| | | Culture | | Total |
|-------|--------------|----------------|----------------|-------|
| | | Positive | Negative | |
| RAT | Positive (+) | True (+) 8 | False (+) 2 | 10 |
| | Negative (-) | False (-) 6 | True (-) 91 | 97 |
| Total | | 14 | 93 | 107 |

Sensitivity:57%; Specificity:97%; PPV:80%; NPV:93% ; Consistency: 90%
RAT:Rapid Antigen Test

Table 4. RAT results in adults

| | | Culture | | Total |
|-------|--------------|----------------|-----------------|-------|
| | | Positive | Negative | |
| RAT | Positive (+) | True (+) 5 | False (+) 4 | 9 |
| | Negative (-) | False (-) 3 | True (-) 101 | 104 |
| TOTAL | | 8 | 105 | 113 |

Sensitivity:62%; Specificity:96%; PPV:55%; NPV:97% ; Consistency: 93%
RAT:Rapid Antigen Test

4. DISCUSSION

We found RAT sensitivity as 62-57%, specificity as 96-97%, PPV as 55-80%, and NPV as 97-93% when we applied RAT and throat culture in adult and pediatric patients having Centor score ≥ 2 in our study. When we compared the HAT and culture outcomes of adult and pediatric patients, the results were clinically similar. Besides, our results regarding test sensitivity and PPV values were much lower than those specified by the manufacturer (sensitivity: 97.3%, specificity: 99%, PPV: 98.6% and NPV: 97.5%).

A rapid, easy and readily available method using throat swab to detect streptococci, RAT, is being used as a diagnostic tool in recent years. This test has advantageous of giving result within minutes during diagnostic study and has a sensitivity of 70-80% and a specificity of 95% when used with the gold standard throat culture test. However, RAT sensitivity may differ between 75% to 95% according to the kit and the study design (14). This variation was thought to arise from study groups, culture methods, laboratory performance and difference in disease spectrum. One of the most important factors affecting test sensitivity is gathering throat swab correctly. The American Academy of Pediatrics (AAP) guideline reports that RAT sensitivity differs between 70%-95% according to the swab gathering technique and staff

experience (15). Besides, colony amount on the swab may affect RAT sensitivity. A number of recent study emphasize that RAT sensitivity varies according to disease severity (16, 17).

When we consider variation in RAT sensitivity, IDSA, AAP, the American Heart Association (AHA) and other recent guidelines recommend verifying negative RAT results with throat culture which has higher sensitivity (18). Studies evaluating RAT and throat culture report RAT sensitivity as 87-96.7%, RAT specificity as 95-100%, PPV as 84.5-95%, and NPV as 95.1-100% (9, 19). Gurol et al. found RAT sensitivity as 64.6% which is much lower than the value (95%) declared by manufacturer, but higher than the value (58%) reported in literature (58%) (20). Çamurdan et al. reported RAT sensitivity as 97.2% in their study and they state that this difference may be originating from the trademark of the kit they used (21). A study by Cardoso et al. demonstrated that PPV of RAT is 44.9% and 32.9% of the cases were prescribed with unnecessary antibiotic (11) The most probable explanation of this low sensitivity in our study depends on various factors that affect RAT sensitivity such as swab collecting technique, variety in staff experience, throat flora of patient at that moment, and inadequate time allowed to each patient in emergency departments, as mentioned in the literature.

Araujo et al. detected a false-positive rate of 32.6% (n=15) and speculated that this had arisen from improper technique of rapid test they used or from cross-reaction of other groups with streptococci. Also, they pointed out that usage of eau for oral hygiene prevents microorganisms to reproduce in culture media properly (22). We found false-positive result in only 3.5% (n=4) of adult group and in 1.8% (n=2) of pediatric group. On the other hand, our study demonstrated that if we didn't administer RAT; clinicians would decide to prescribe unnecessary antibiotics to 43.3% (n=49) of adults and 54.2% (n=58) of pediatric patients according to clinical findings. Consequently, usage RAT precludes prescription of unnecessary antibiotics especially in pediatric patients.

Mayes et al. point out the fact that if false-negative rate of RAT decrease below 2.4%, it can replace throat culture (23). According to Infectious Diseases Society of America (IDSA), because streptococcal pharyngitis and acute rheumatic fever are very rare for children < 3 years old, there is no need for further diagnostic studies in this age group except for selected children in GABHS pharyngitis (24). But Çamurdan et al. reported false-negative rate of RAT as 6.1% which is lower than that of many previous studies, and stated that negative test results should be verified with throat culture in countries where GABHS infection complications are frequently encountered such as Turkey (21). The study by Araujo Filho et al. reported NPV of RAT as 94.2% and 6% (n=2) false-negative result. They speculated that this might originate from restricted amount of antigens located in oropharynx (22). Darrow et al. proposed the explanation of RAT negativity in culture (+) patients as insufficient amount of swab material collection during RAT procedure, besides rarely presence of scarce amount of colonies in culture

media (25). We found false-negative RAT result rate only 2.6% (n=3) among adults and 5.7% (n=6) in pediatric group. Thus, only 9 in 220 patients (4%) did not receive antibiotic treatment although they needed. Throat culture results were followed-up and patients with positive culture results were recalled. Hence, it is important to keep in mind that RAT results should be re-evaluated concomitantly with culture results especially in countries where RAT sensitivity is low and affected by many factors, and GABHS infection and its complications are frequently encountered like our country.

There is no international consensus currently on RAT usage in streptococcal tonsillopharyngitis diagnosis. Nonetheless, these kits are being commonly used in Europe and United States (26). There are a number of advantages of RAT though variations in its sensitivity rates. Application of this test in laboratory, clinics and emergency departments is easy which give result in less than 15 minutes. In this way, RAT provides rapid and reliable diagnosis of GABHS and decrease nonsuppurative complications of the infection and precludes unnecessary antibiotic prescription rates (20). Maltezou et al. reported 61% decrease in unnecessary antibiotic prescription rate with RAT use (12). Improper antibiotic usage leads to drug side effects, antibiotic resistance development, and consequent increase in health service cost. Rapid antigen test can provide economic gain in health expenditures if its sensitivity is high enough (27).

Limitations of this study;

- 1- The cost of throat culture test performed at emergency departments is not included in health insurance in our country. Also, RAT cost is relatively high which limits patient number included into study.
- 2- The factors that affect oral flora (such as oral hygiene, smoking, use of eau for oral hygiene, etc.) were not evaluated during throat swab collection which was done and evaluated at emergency department by unstandardized various health staff. This might influence test results.
- 3- The participants had not been followed-up in terms of drug side effects, antibiotic resistance, or hospital re-admission. Thus, we could not make an extensive calculation of cost effectiveness.

5. CONCLUSION

We found lower sensitivity and PPV of RAT in patients admitted with acute tonsillopharyngitis than those declared by the manufacturer and by previous studies in the literature. Whereas, our RAT specificity and NPV of RAT were higher than those reported before. Thus, low levels of sensitivity decrease the possibility of RAT to be a diagnostic tool for the diagnosis of GABHS. But all factors affecting RAT sensitivity should be kept in mind. Additionally, low false-positivity rate of RAT decreases unnecessary antibiotic prescription tendency of doctors at emergency department who decide according to clinical criteria only. Further extensive studies

with higher patient population are needed to clarify the benefits of RAT use in GABHS diagnosis.

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