Impact of the rapid antigen detection test in diagnosis and treatment of acute pharyngotonsillitis in a Pediatric emergency room

Impacto do uso da prova rápida para estreptococo beta-hemolítico do grupo A no diagnóstico e tratamento da faringotonsilite aguda em pronto-socorro de Pediatria

Impacto del uso de la prueba rápida para estreptococos beta-hemolíticos del grupo A en el diagnóstico y tratamiento de la faringotonsilitis en emergencia de Pediatría

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ABSTRACT

Objective: To evaluate the impact of the routine use of rapid antigen detection test in the diagnosis and treatment of acute pharyngotonsillitis in children.

Methods: This is a prospective and observational study, with a protocol compliance design established at the Emergency Unit of the University Hospital of Universidade de São Paulo for the care of children and adolescents diagnosed with acute pharyngitis.

Results: 650 children and adolescents were enrolled. Based on clinical findings, antibiotics would be prescribed for 389 patients (59.8%); using the rapid antigen detection test, they were prescribed for 286 patients (44.0%). Among the 261 children who would not have received antibiotics based on the clinical evaluation, 111 (42.5%) had positive rapid antigen detection test. The diagnosis based only on clinical evaluation showed 61.1% sensitivity, 47.7% specificity, 44.9% positive predictive value, and 57.5% negative predictive value.

Conclusions: The clinical diagnosis of streptococcal pharyngotonsillitis had low sensitivity and specificity. The routine use of rapid antigen detection test led to the reduction of antibiotic use and the identification of a risk group for complications of streptococcal infection, since 42.5% positive rapid antigen detection test patients would not have received antibiotics based only on clinical diagnosis.

Key-words: tonsillitis/diagnosis; *Streptococcus* group A; child; adolescent.

RESUMO

Objetivo: Avaliar o impacto da realização rotineira da prova rápida para pesquisa de estreptococo do grupo A no diagnóstico e tratamento da faringotonsilite aguda em crianças.

Métodos: Estudo prospectivo e observacional que contou com a utilização de protocolo de pesquisa estabelecido na Unidade de Emergência do Hospital Universitário da Universidade de São Paulo para o atendimento de crianças e adolescentes com faringotonsilite aguda.

Resultados: Com base na avaliação clínica, dos 650 pacientes estudados, antimicrobianos seriam prescritos para 389 indivíduos (59,8%) e, com o uso da pesquisa de estreptococo do grupo A, foram prescritos em 286 pacientes (44,0%). Das 261

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crianças que não receberiam antibiótico pelo quadro clínico, 111 (42,5%) tiveram pesquisa de estreptococo do grupo A positiva. O diagnóstico baseado no quadro clínico apresentou sensibilidade de 61,1%, especificidade de 47,7%, valor preditivo positivo de 44,9% e valor preditivo negativo de 57,5%.

Conclusões: O diagnóstico clínico da faringotonsilite estreptocócica mostrou baixa sensibilidade e especificidade. O uso rotineiro da prova rápida para pesquisa de estreptococo permitiu a redução do uso de antibióticos e a identificação de um grupo de risco para as complicações da infecção estreptocócica, pois 42,5% dos pacientes com prova rápida positiva não receberiam antibióticos, se levado em consideração apenas o diagnóstico clínico.

Palavras-chave: tonsilite/diagnóstico; *Streptococcus* grupo A; criança; adolescente.

RESUMEN

Objetivo: Evaluar el impacto de la realización de rutina de la prueba rápida para investigación de estreptococos del grupo A en el diagnóstico y tratamiento de la faringotonsilitis aguda en niños.

Métodos: Estudio prospectivo y observacional que contó con el uso de protocolo de investigación establecido en la Unidad de Emergencia del Hospital Universitario de la USP para la atención a niños y adolescentes con faringotonsilitis aguda.

Resultados: Con base en la evaluación crítica, de los 650 pacientes estudiados, antimicrobianos serían prescritos a 389 individuos (59,8%) y, con el uso de la investigación de estreptococos del grupo A se los prescribieron a 286 pacientes (44,0%). De los 261 niños que no recibirían antibióticos por el cuadro clínico, 111 (42,5%) tuvieron investigación de estreptococos del grupo A positiva. El diagnóstico basado en el cuadro clínico presentó sensibilidad del 61,1%, especificidad del 47,7%, valor predictivo positivo del 44,9% y valor predictivo negativo del 57,5%,

Conclusiones: En este estudio, el diagnóstico clínico de la faringotonsilitis estreptocócica mostró baja sensibilidad y especificidad. El uso de rutina de la prueba rápida para investigación de estreptococos permitió la reducción del uso de antibióticos y la identificación de un grupo de riesgo para las complicaciones de la infección estreptocócica, pues el 42,5% de los pacientes con prueba rápida positiva no recibirían antibióticos si se llevara en consideración solamente el diagnóstico clínico.

Palabras clave: tonsilitis/diagnóstico; estreptococos del grupo A; niño; adolescente.

Introduction

Acute pharyngotonsillitis is a common disease in pediatric patients. It is caused by various etiological agents, and the frequency of each of them varies according to the age of the child, the season of the year, and the geographical area[1]. Viruses are the most common etiological agents[2-4]. Among the bacterial agents of pharyngotonsillitis, the beta-hemolytic streptococcus of Lancefield group A (GABHS) is responsible for 15 to 30% of cases[2-11].The natural course of pharyngotonsillitis caused by GABHS is self-limited, in most cases, with resolution of signs and symptoms between 2 and 5 days[6]. Antibiotic therapy is indicated to reduce illness duration and morbidity and to prevent suppurative complications, transmission of GABHS (after 24 hours of antibiotics there is no transmission of the bacterial agent), and non-suppurative complications (rheumatic fever)[2,6,7].

It is difficult to differentiate viral from bacterial etiology[1-4,8] only through clinical signs and symptoms. In 1981, Centor *et al*[11] proposed a clinical model to determine the probability of streptococcal infection in adult patients who sought an emergency department with a history of sore throat and fever. The model consisted of an evaluation of four clinical variables: tonsillar exudate, painful cervical lymphadenopathy, fever, and absence of cough. Patients with four variables had a 56% probability of positive oropharyngeal culture for GABHS; three variables, 32%; two, 15%; one, 6.5%; and none, 2.5%[11]. Over the years, several authors have adopted the scoring system as selection criterion for the diagnosis and treatment of acute pharyngotonsillitis. The criteria used by Centor *et al* started to be modified and used as a basis for the definition of new clinical scores for the diagnosis of pharyngotonsillitis, especially in pediatric patients. However, the scores described variation in sensitivity from 12 to 93% and specificity from 30 to 93%[4,6,10,12-17]. As a result, the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association, the American Academy of Pediatrics, the American Society of Pediatrics and, more recently, the Brazilian Society of Pediatrics recommend that the diagnosis of pharyngotonsillitis in patients with clinical and epidemiological suspect of infection by GABHS be confirmed through the use of microbiological techniques[3,4,6,15,17-20].

Among the microbiological methods available, the culture of oropharyngeal secretion is the gold standard for the diagnosis of group A streptococcal pharyngotonsillitis[8,17-19,21]. It presents a sensibility of 90 to 95% for the detection of GABHS[17], however, the time of sowing

secretion should be more than 24 hours, with result reading from 24 to 48 hours[2,17]. The rapid antigen detection test (RADT) for GABHS is an immunoassay for the detection of etiological antigens in oropharynx. It presents specificity of around 95%[2-4,8,21-24], however, its sensitivity ranges from 87.0 to 96.7%[2-4,8,24].

In 2006, Cardoso *et al* conducted a prospective study in the emergency unit of Hospital Universitário da Universidade de São Paulo (USP) to compare clinical and microbiological diagnoses in children with acute pharyngotonsillitis. The authors' conclusion was that the clinical examination, without the use of microbiological techniques, is insufficient to detect pharyngotonsillitis caused by GABHS[3]. From April 2008, a protocol of assistance for patients with suspected acute pharyngotonsillitis was instituted as routine in this service, based on the commendations of the Brazilian Society of Pediatrics[25]. Children older than 2 years old, complaining of sore throat, fever, and no signs of viral infections, started to be submitted to the collection of rapid test for GABHS. In children with negative RADT, a new swab is collected to perform oropharynx culture and wait for the result without the introduction of antibiotics. In cases in which the RADT is positive, a treatment with antibiotics is started.

Although the use of microbiological techniques for the diagnosis and treatment of pharyngotonsillitis is recommended by the Brazilian Society of Pediatrics[25], there are no studies in the country that evaluates the usefulness of this procedure in the emergency unit. Therefore, the aim of this study was to assess the impact of routine use of rapid strep test in the diagnosis and treatment of children and adolescents with acute pharyngotonsillitis.

Method

We conducted a prospective observational study of the assistance protocol established in the pediatric emergency unit of Hospital Universitário da Universidade de São Paulo, from April to November, 2008. The study was approved by the Research Ethics Committee of Hospital Universitário da Universidade de São Paulo.

The University Hospital — Hospital Universitário da Universidade de São Paulo — assists the general public. At the pediatric emergency unit, the staff consists of assistant physicians linked to the Department of Pediatrics of the School of Medicine – USP, of physicians in charge of medical care and supervision of pediatric residents and intern students attending the 5th year.

The children were assessed by the examiner. Inclusion criteria for analysis in the study were: age between 2 and 15 years; history of sore throat and fever; no signs of viral infection (cough, nasal congestion, watery eyes and diarrhea), except for runny nose, when it was the only symptom. Exclusion criteria were: use of antibiotics in the last 24 hours or RADT with negative results without collection of oropharyngeal cultures.

The results of RADT for GABHS were evaluated. The test used was the Clearview Strep A® (Oxoid), which consists of a rapid immunoassay for the qualitative detection of group A streptococcal antigens. The material examined was oropharynx secretion. We used a swab carefully introduced into the oropharynx as not to touch the cheek mucosa, tongue or uvula. Then, with a vigorous movement, the secretion in the tonsils was collected. The rapid test was performed immediately, using a methodology according to the manufacturer's recommendations. The examinations were collected by the physicians responsible for the treatment of the child or by a nurse, all previously trained. When the RADT showed negative results, we proceeded to the collection of the culture of oropharyngeal secretions, following literature recommendations in order to minimize misinterpretations caused by collection with improper technique. After collection of the exams, the following data about the patient were filled: name (initials) of the child; age; date of visit; and result of RADT for group A streptococcus. Three questions were directed to the physician who treated the child:

- Are there signs of upper respiratory tract infections?
- Would you indicate antibiotics due to clinical data?
- Did you prescribe antibiotics after the exam?

We evaluated the demographic characteristics of the study population (age and sex) and the etiologic agents with growth in oropharyngeal cultures. To determine the performance of the RADT in the various age groups, patients were divided into younger than 60 months and older than 60 months. The oropharynx culture was considered negative when: there was no identification of any etiologic agent, there were agents of the normal bacterial flora of the oropharynx *(S. viridans)* or etiologic agents non-causative of tonsillitis (*Haemophilus* spp, Neisseria spp. *Streptococcus pneumoniae*). The oropharynx culture was considered positive when the following etiologic agents were identified: *Streptococcus pyogenes*, groups G, F, and C beta hemolytic Streptococci, beta hemolytic Streptococci unfeasible for identification of serogroups, and nontypable beta hemolytic Streptococci.

There was no sample size calculation. A sample of convenience was used during the study period. Descriptive statistics was used to present the continuous variables collected as mean, median, and standard deviation, and as proportions, histograms, and frequency tables for categorical variables. Comparisons between categorical variables were made by chi-square or Fisher exact test, where applicable. Comparisons between continuous variables with parametric distribution were performed with Student's *t* test or ANOVA, and nonparametric comparisons, with the Mann-Whitney test. The level of significance was 0.05. The statistical packages used were SPSS PASW Statistics 17.0 and WINKS SDA 6.0.9 from Windows Kwistat, demo version.

Results

The present study assessed 673 patients, and 20 were excluded because they were under 2 years old. The study included 653 children, but in three of them there was no proper record of data. Thus, 650 children were assessed.

The sex distribution showed: 327 male children (50.3%) and 323 (49.7%) female. Regarding age, 242 (37.2%) were from 24 to 60 months old and 408 (62.8%) were older than 60 months, being 259 (39.9%) from 60 to 120 months old, and 149 (22.9%) older than 120 months. The rapid test was positive in 286 cases (44%).

Table 1 - Comparison of the results of rapid antigen detection test and intentions of antibiotic administration by the doctor according to the child's clinic

Should the child take antibiotics according to the clinic?	Result of the RADT		*p*-value
	Positive	Negative	
Yes (389 cases)	175 (44.9%)	214 (55.1%)	0.57
No (261 cases)	111 (42.5%)	150 (57.5%)	

The comparison of the RADT results with the intention of antibiotics administration by the physician based only on clinical data is shown in Table 1. There was no significant relationship between the result of RADT and the clinical diagnosis. When considering the result of RADT as the gold standard for the diagnosis of pharyngotonsillitis by GABHS, the medical indication by the clinic would have a sensitivity of 61.1% (175/286), specificity of 47.7% (150/314), predictive positive value of 44.9% (175/389) and negative predictive value of 57.55% (150/261).

Table 2 shows the correct diagnosis according to age group. It was found that there was no significant difference in accuracy between the age groups studied.

Discussion

The GABHS is the main causative bacterial agent of acute pharyngotonsillitis, with a prevalence of 15 to 30%[2-5,25,26]. Although the viral etiology is the most common, pharyngotonsillitis is commonly treated with antibiotics[2,4,7]. In this study, a prevalence of infection by GABHS of 44% was observed, higher than that described in other studies[4,22]. However, a similar result was described by Morais *et al*, who reported a prevalence of 43% of tonsillitis by GABHS in children[26].

Pharyngotonsillitis caused by beta-hemolytic group A streptococcus is more frequent in children above 5 years old and who show clinical evidence of bacterial disease (fever, odynophagia, headache, vomiting and abdominal pain; hyperemia, hypertrophy and purulent exudate in tonsils; painful anterior cervical lymphadenopathy; and soft palate petechiae) and absence of signs and symptoms of upper respiratory tract infections (cough, runny nose, watery eyes, upper airway obstruction, and diarrhea)[9]. In this study, there was statistical significance when the positivity of RADT was assessed according to age greater than 60 months. However, the RADT was positive in 31.8% of children younger than

Table 2 - Comparison of the results of the positive rapid antigen detection test, indication of antibiotics by the doctor, and correct clinical diagnosis in the age groups from 24 to 60 months and older than 60 months

Variables		24 to 60 months n=242	>60 months n=408	*p*-value
Positive rapid antigen detection test		91 (37.6%)	195 (47.7%)	0.011
Indication of antibiotics by the doctor	Yes	143 (59.0%)	246 (60.0%)	0.762
	No	99 (41.0%)	162 (40.0%)	
Correct clinical diagnosis	Yes	118 (48.8%)	207 (50.7%)	0.627
	No	124 (51.2%)	201 (49.3%)	

60 months, suggesting the need to conduct the examination also in these patients. It is believed that tonsillitis caused by GABHS is less prevalent in the age group younger than 5 years due to the high incidence of viral infections in this age group, besides lower adherence of the bacteria to the tonsillar epithelium. Other authors also identified GABHS in 30% of tonsillitis in children aged less than 60 months, especially at ages 24 to 36 months[26,27].

The clinical and epidemiological data did not show sufficient sensitivity and specificity for the diagnosis of pharyngotonsillitis caused by GABHS. Since the 1970s, numerous authors in many countries have tried to establish a clinical score with high sensitivity and specificity to detect streptococcal pharyngotonsillitis, however, without success[1,4,6,7,10,12-17]. The initial clinical evaluation, based on clinical and epidemiological findings and performed by physicians who treated the children, generated inadequate clinical diagnosis in 50% of cases, which corroborates data presented in the literature. Such data demonstrate that the clinical evaluation, without the use of microbiologic techniques, is an inaccurate diagnostic tool to identify Group A streptococcal pharyngotonsillitis[3].

In this study, antibiotics would have been unnecessarily prescribed in 32.9% of cases. Similar studies also show the decrease in the use of antibiotics when RADT is used as a diagnostic tool[8]. The unnecessary prescription of antibiotics generates increased bacterial resistance, besides the risk of adverse effects that may occur from exposure to these medications. Interventions to reduce inadvertent prescription of antibiotics should be provided, and the use of microbiological diagnostic techniques, such as RADT, is one of the recommended interventions[28].

On the other hand, in 17.1% of cases, if the clinical assessment were used as a sole diagnosis method, patients with pharyngotonsillitis by GABHS would no longer receive antibiotics. With that, they would be at risk of suppurative and non-suppurative complications. Rheumatic fever is very prevalent in developing countries[29]. In Brasil, between 2005 and 2007 around 30,000 patients required hospitalization for treatment of rheumatic fever, which cost R$162,000.00 to the National Health System. Among the cardiac surgeries performed in Brazil, 26% are directed to correction of rheumatic valve disease[30].

Studies similar conducted in other countries also demonstrated difficulties for the empirical therapeutic decision in cases of pharyngotonsillitis. In such analyses, the availability of the use of RADT for GABHS in the diagnosis of acute tonsillitis allowed reduction in the prescription of antibiotics and ensured that the children with infection by GABHS were treated early, reducing, therefore, the risk of late complications[8,26,31,32]. There results corroborate, therefore, literature data that mention that for the adequate diagnosis and treatment of tonsillitis by GABHS, only the clinical evaluation based on signs and symptoms is a poor diagnostic tool.

The diagnosis should be based on clinical and epidemiological suspicion, confirmed by microbiological method to early identify the etiological agent. The rapid antigen detection test for EBGA is a rapid immunoassay for the detection of carbohydrate antigens of group A of the etiologic agent in the oropharynx. Due to its high specificity, it is recommended that in cases where the RADT is positive, concomitant oropharynx culture should not be performed[22]. On the other hand, due to the varying sensitivity according to the intensity of the disease, inadequate collection technique, low amount of antigens and type of kit used[18,20,22,24], in case of a negative rapid test, it is recommended that oropharynx culture be collected[2,24,26,27,32]. Various studies were performed to compare the RADT and oropharynx culture, and it was observed that the sensitivity of RADT varies from 87.0 to 96.7%; specificity, from 95.1 to 100.0%; the positive predictive value, from 84.9 to 95.0%; and the negative predictive value, from 93.8 to 98.9%[2-4,8,24].

This study has some limitations. Firstly, the analysis did not use a standardized clinical score for the diagnosis of tonsillitis. Such option was made because the main goal was to reproduce the most frequent practices in everyday clinic, and not to compare the diagnostic methods per score versus the microbiological method. However, data on clinical history and physical examination were adopted as inclusion criteria, which are invariably mentioned in most existing scores. Secondly, the clinical evaluation and sample collection were performed by different professionals each time. This, certainly, hinders the uniformity of the data. However, the service performed by students was supervised by an assistant physician or a resident. Moreover, in all negative RADTs occurred the collection of oropharynx culture, reducing the possibility of false-negative results. Another limitation is not having done the cost-effectiveness analysis of adopting a protocol with RADT, but, undoubtedly, the reduction on the use of

antibiotics is an important benefit for the child and for the health service, besides the possible impact on selective pressure of antimicrobial resistant strains.

In the present study, the clinical diagnosis of streptococcal pharyngotonsillitis presented low sensitivity and specificity, which had already been demonstrated in several previous studies. The rapid antigen detection test proved to be a good screening tool for the diagnosis of streptococcal pharyngotonsillitis, once it allowed the reduction of antibiotics and the identification of a risk group for complications of streptococcal infection. Therefore, the routine use of RADT allows a more accurate etiologic diagnosis.

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