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Clinical Usefulness of a Rapid Antigen Test in Patients with 2009 H1N1 Influenza

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We read with interest the article by Choi, et al.[1] (RA1), entitled "The clinical usefulness of the SD bioline influenza antigen test for detecting the 2009 influenza A (H1N1) virus." In this study, the authors explained that the rapid antigen test (RAT) cannot be recommended for general use in all patients with influenza-like illnesses because of its low sensitivity. However, there were two very similar previous reports (RA2 Choi, et al.,[2] RA3 Lee, et al.[3]) that demonstrated high RAT sensitivity with the same RAT kit previous to the results presented by Choi, et al.[1] (RA1). The sensitivity of the two previous reports was above 75.6%.

RAT kits are used to screen patients with suspected influenza and offer the advantage of providing a timely result that can influence clinical decision making.[4] RAT can be used in many hospital laboratories, emergency departments, and private clinics easily. RAT can also help to reduce unnecessary diagnostic testing, facilitate antiviral treatment, and decrease the inappropriate use of antibiotics. However, the clinical sensitivity of RAT has been shown to be poor for 2009 H1N1 influenza, demonstrating an accuracy of 11.1% to 51%.[4] Also, viral concentrations in clinical samples can influence the sensitivity of RAT. Thus, the collection time of the samples may be an important factor for the accuracy of RAT.[5]

We compared two previous reports on RAT sensitivity and specificity. We used the real-time reverse transcription-polymerase chain reaction to confirm the 2009 H1N1 influenza using nasopharyngeal or throat swap sample. RAT was performed using the SD Bioline Influenza A/B/A (H1N1) Pandemic kit (Standard Diagnosis, Inc., Suwon, Korea). There are four detection lines of the RAT; influenza A, influenza B, 2009 H1N1, and control (1). Samples were classified according to the hours that elapsed after the first symptoms appeared to when they were collected in RA1 and RA3. They were classified into ≤24 hours (D1), 24 to 48 hours (D2), 48 to 72 hours (D3), and after (D4) in RA1, and ≤24 hours (D1), 24 to 48 hours (D2), 48 to 72 hours (D3), 72 to 96 hours (D4), and 96 to ≤168 hours (D5) in RA3. RA2 did not analyze the time-dependent sensitivity of RAT.

The overall sensitivity of RAT was 44% for RA1 (117/266), 77.0% for RA2 (241/313), and 75.6% for RA3 (482/637). The specificity of RAT was 99.9%, 100% and 99.3%, respectively. The positive predictive value (PPV) were 99.2% (RA1) and 100% (RA2). The negative predictive value (NPV) were 81.8% (RA1) and 86% (RA2). The time dependent sensitivity of RAT at D1, D2, D3, D4-5 was

61.3%, 67.9%, 51.1%, and 11.1% in RA1 and 75.0%, 76.8%, 79.9%, 77.4%, 67.3% in RA3.

Early diagnosis and treatment is very important to treating influenza, because if the diagnosis is delayed, complications can increase. In particular, the 2009 H1N1 influenza virus involves the lower respiratory tract, which can lead to pneumonia. Choi, et al. (RA1) insist that the RAT kit cannot be recommended for general use in all patients with influenza-like illness because of its low sensitivity. However, the sensitivity of the SD Bioline Influenza A/B/A (H1N1) Kit was relatively good in the two previous studies. The sensitivity of RAT was relatively high in RA2 (77.0%) and RA3 (75.6%). The time-dependent sensitivity of RAT was evaluated to increase the sensitivity in RA1 and RA3. Through these results we can increase the sensitivity of the RAT kit to detect influenza virus in clinical settings everywhere.

The RAT kit is known as a point-of-care test, because they have a fast turnaround time within 30 minutes and require minimal training to perform. However, major problem of RAT was low sensitivity for H1N1 virus. In this study, according to the results of RA2 and RA3, we can use the SD Bioline Influenza A/B/A (H1N1) Kit in general clinical settings with relatively high sensitivity, convenience, rapidity, portability, and ease of performance in all situations. To know the exact sensitivity of the SD RAT kit, we need further studies with more samples. However, we suggest that the SD Bioline Influenza A/B/A (H1N1) Kit can be used in general clinical settings for cases where samples are obtained from patients who visit a hospital within 72 hrs of symptom onset, because three studies have reported relatively high sensitivity of at least 60.4% (RA1).

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AUTHOR'S REPLY

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To the editor,

We are grateful for the comments on the issue of the clinical usefulness of the rapid antigen test (RAT) for influenza. The RAT has an advantage of providing clinicians with an answer within minutes. However, the usefulness of the test is debatable due to its inconsistent accuracy and, especially, its highly variable sensitivity.

In our report, the sensitivity of the SD Bioline Influenza Antigen Test® (Standard Diagnostic, Inc., Suwon, Korea) was 44.0% and the specificity was 99.9%.[1] The RAT kit used in our study was developed for seasonal influenza virus circulating before the 2009 pandemic influenza and was not specialized for the A(H1N1)pdm09 virus. In comparison, the SD Bioline Influenza Antigen A/B/A (H1N1) Pandemic® kit (Standard Diagnostic, Inc., Suwon, Korea), which was used in the other two studies, was developed for the specific detection of the A(H1N1)pdm09 virus.[2,3] Therefore, a head-to-head comparison of our study and the other two studies is inappropriate. The new test kit may have improved accuracy for detecting A(H1N1)pdm09 virus.

A point to be considered, other than the difference of the RAT kits, is careful interpretation of the RAT results in terms of deciding antiviral treatment or infection control measures. With a positive result of the RAT, a clinician can confidently diagnose influenza and begin antiviral therapy as well as appropriate infection control measures because the specificity of the RAT is very high. However, a negative result of the RAT has a reasonable likelihood of being false negative even if the sensitivity of the test is 77.0%. If a negative result is reported by the RAT in a patient with an influenza-like illness and who is at a high risk for developing influenza complications, a clinician cannot exclude influenza and defer the initiation of antiviral therapy or infection control measures either. That is, a clinician comes to deciding on initiating early antiviral therapy or infection control measures, especially for high risk patients, on the basis of

clinical judgment regardless of the result of the RAT. Of course, other diagnostic tests, real-time reverse transcriptase polymerase chain reaction (rRT-PCR) or viral culture, have their own limitations. Their most obvious limitation is the longer time required for reporting results. Antiviral therapy is most effective when it is initiated within 48 hours after onset of influenza symptoms.[4,5] Infection control measures should be initiated immediately after recognition of an influenza case, because influenza viruses can be transmitted from the day before symptoms begin.[6] For the best management of influenza patients, antiviral therapy or infection control measures cannot be delayed while the results of rRT-PCR or viral culture are awaited. Requiring high cost, specialized equipment and expertise is another disadvantage of these tests. When considering the limitations of laboratory diagnostic tests, recent guidelines for influenza management recommended that antiviral therapy should not be delayed while waiting for a definitive influenza test result and negative results from RAT should not be used to make treatment or infection-control decisions.[7-9]

The influenza A (H3N2) virus was the predominant influenza virus subtype during the 2011-2012 season in Korea, up to the 8th week of 2012.[10] For recommending the RAT in general clinical settings, therefore, we should consider the usefulness of the RAT in detecting seasonal influenza virus as well as the A(H1N1)pdm09 virus. Yoo, et al.[11] reported that the sensitivity of the SD Bioline Influenza Antigen Test® (Standard Diagnostic, Inc., Suwon, Korea) was 61.9% for the influenza A virus and 54.5% for the influenza B virus, respectively. A meta-analysis including several RAT kits also reported a low sensitivity for RAT as 62.3% (95% CI, 57.9% to 66.6%) and concluded that influenza can be ruled in but not ruled out through the use of RAT.[12]

In conclusion, though the RAT has some advantages, we still hold the viewpoint that RAT results need to be interpreted carefully in general clinical practices and development of improved RAT kits or other diagnostic methods is necessary.

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