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Accuracy and Cross-Reactivity of Rapid Diagnostic Tests for Norovirus and Rotavirus in a Real Clinical Setting

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ABSTRACT

Background: Rapid diagnostic test (RDT) of norovirus and rotavirus is commonly used for outbreak screening and patient management. Varying accuracy of the test and cross-reactivity has been reported and could affect the outcome of management. The primary purpose of this study is to provide the accuracy of norovirus and rotavirus rapid diagnostic tests and to analyze the cross-reactivity of both tests.

Materials and Methods: Stool samples collected from every acute diarrhea patient aged <15 years old who was admitted at Bhumibol Adulyadej Hospital, Bangkok, Thailand, from November 2014 to September 2016 underwent the following test: QuickNaviTM – Norovirus2 for norovirus, VIKIA® Rota-Adeno for rotavirus, and aerobic bacterial culture. Real-time reverse transcription polymerase chain reaction was used as a gold standard for virus detection. False-positive results determined cross-reactivity.

Results: From 358 stool specimens, the sensitivity of RDTs for norovirus and rotavirus was 27.5% and 44.8%, respectively. The specificity of RDTs for norovirus and rotavirus was 97.7% and 91.6%, respectively. False positive results of RDT for norovirus occurred in 6 samples (1.7%) and 22 samples (6.1%) in RDT for rotavirus. Rotavirus RDT was found to have cross-reactivity with 11 norovirus infection and 3 bacterial infected stools.

Conclusion: We found that the RDTs for both rotavirus and norovirus have high specificity but low sensitivity. Cross-reactivity was observed in positive rotavirus RDT with half of it being norovirus.

Keywords: Norovirus; Rotavirus; Rapid diagnostic test; Accuracy; Cross-reactivity

INTRODUCTION

Acute gastroenteritis is one of the most common problems in healthcare. Norovirus, a non-enveloped single-stranded RNA virus of the *Caliciviridae* family, is responsible for approximately 900,000 outpatient visits and 64,000 admissions in children <5 years in developing countries per year [1, 2]. Norovirus has 7 genogroups (GI to GVII) with GI and GII responsible for human infection [2, 3]. Similarly, rotavirus infects approximately 114 million people per year, with 2.3 million cases needing hospitalization and resulting in the death of >200,000 children under 5 years of age [4]. Rotavirus is a non-enveloped double-stranded RNA virus of the *Reoviridae* family with genogroup A as the dominant group in human infection.

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Nowadays, immunochromatographic (IC) test is commonly used as a rapid diagnostic test (RDT) because it is easier and faster to apply comparing to other diagnostic tests. It is used for the purpose of epidemiology outbreak studies and patient management. The sensitivity and specificity of norovirus RDTs are 24 - 100% and 62 - 100%. Rotavirus RDT are stated to range from 69 - 94% and 84 - 100%, in sensitivity and specificity, respectively [5-13]. In Thailand, the sensitivity and specificity of norovirus RDT range from 74.2 - 83.3% and 87.5 - 99.5% respectively. A study of rotavirus rapid tests showed 93.6% sensitivity and 96.17% specificity [8, 14, 15]. Also, a report of cross-reactivity is rare between rotavirus and norovirus, as mentioned in previous reports [5, 6, 10, 16-19]. While the range of accuracy of these kits is still not consistent, physicians can sometimes misunderstand rotavirus and norovirus' rapid diagnostic test as a complete tool for diagnosing patients with gastroenteritis. It can mislead management. Therefore, the primary outcome of this study is to provide the accuracy of rotavirus and norovirus RDT in pediatric patients with acute gastroenteritis. The secondary outcome is to find the cross-reactivity between rotavirus and norovirus RDT.

MATERIALS AND METHODS

Stool samples were collected from every pediatric patient aged <15 years old who were diagnosed with acute gastroenteritis and admitted at Bhumibol Adulyadej Hospital, Bangkok, Thailand during November 2014 to September 2016. The samples were retrieved using sterile plastic containers. The fresh stool samples were immediately used to perform the following tests; RDT for norovirus (using QuickNavi™ – Norovirus2, Denka Seiken, Tokyo, Japan), rapid diagnostic test for rotavirus (using VIKIA® Rota-Adeno, BioMérieux, Craponne, France) and stool aerobic bacterial culture at Bhumibol Adulyadej Hospital laboratory. The method of specimen preparation and test was according to the manufacturer's manual. Each stool sample was then stored at -20°C and further transferred to the Biological Institute, Department of Medical Science, Ministry of Public Health, Bangkok, for gold standard testing of norovirus and rotavirus using real-time reverse transcription polymerase chain reaction (RT-PCR) and conventional RT-PCR every month. Viral nucleic acids were extracted from fecal suspension and submitted to real-time RT-PCR and conventional RT-PCR using Ag-Path-ID 1 strep RT-PCR kit (Applied Biosystems, Foster City, CA, USA) and the 7,300 Real-Time PCR system (Applied Biosystem, USA). The norovirus real-time RT-PCR was carried out using primers COG1F/COG1R and COG2F/COG2R. The minimum quantitative of Noro real time RT-PCR assay was determined as 1.0×10^2 copies/PCR reaction tube. Then, Positive real-time RT-PCR samples underwent further investigation to determine genotype using conventional RT-PCR. Primer G1SKF/G1SKR and G2SKF/G2SKR were used to target the specific norovirus region located in the RdRp of ORF1 -ORF2 junction.

The study was conducted with the approval of the Ethical Committee of Bhumibol Adulyadej Hospital (Serial No. 10/60).

Results of the index and reference tests were recorded in an Excel database (MS Corporation, Seattle, WA, USA). The data were analyzed for the primary outcome. Sensitivity, specificity, and accuracy of QuickNavi™ – Norovirus2 and VIKIA® Rota-Adeno were calculated by using RT-PCR as the gold standard method. Statistical analyses were performed using SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA). Cross-reactivity was determined from false positive results.

RESULTS

From the period of 21 months, 358 stool samples were collected. The median age of patients is 14.6 months with interquartile range of 19.5 months. Twenty four patients had multiple stool samples of 55. Five patients had repeated exams in the same hospital visit with an average interval time of 4 days. Five patients had more than 2 stool samples from different hospital visits (3 visits = 3 patients, 4 visits = 2 patients). Norovirus was found in 102 stool samples, with 3 common genotypes; GII.3, GII.4, and GII.17. Rotavirus was found in 96 samples. The aerobic bacterial culture was positive in 43 samples. Co-infection between rotavirus and norovirus was determined in 21 samples as shown in **Figure 1**.

1. Sensitivity & specificity

The sensitivity of RDTs for norovirus and rotavirus was 27.5% (28/102), and 44.8% (43/96), respectively and sensitivity tends to improve when excluded rotavirus and norovirus co-infection. The specificity of RDTs for norovirus and rotavirus was 97.7% (250/256) and 91.6% (240/262), respectively. When differentiated into age groups of <5 years old and >5 years old, the sensitivity and specificity slightly changed, as shown in **Table 1**. The RDT for norovirus gave the positivity rate of Group II infection as 31.7% but could not detect Group I and GII.17. The test had the best sensitivity for detection of genotype GII.4 (48.9%, including 2 cases of co-infection with GI.5 and GI.15) while non-GII.4 sensitivity was 10.5% as shown in **Table 2**. Please see **Supplementary Table 1**-**6** for more information.

2. Negative predictive value (NPV) & positive predictive value (PPV) and accuracy

RDT for norovirus has NPV of 77.2% (250/324) and PPV of 82.4% (28/34). Whereas, RDT for rotavirus has NPV and PPV of 81.9% (240/293) and 66.2% (43/65), respectively. RDT for
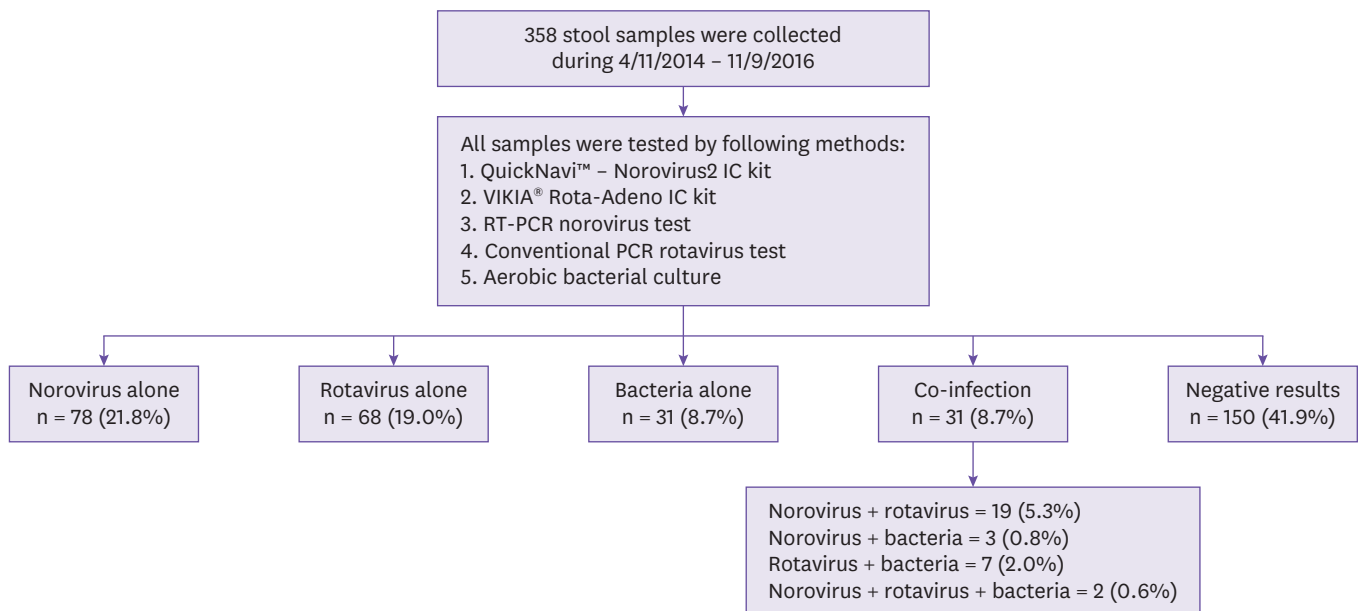

Figure 1. Method diagram. Stool samples were collected from 4 November 2014 to 11 September 2016.
All samples were tested by 5 methods (QuickNavi™ – Norovirus2 IC kit, VIKIA® Rota-Adeno IC kit, RT-PCR norovirus test, Conventional PCR rotavirus test, and aerobic bacterial culture). Total number of norovirus, rotavirus and bacteria are 102 (28.5%), 96 (26.8%) and 43 (12.0%) samples respectively. This diagram is categorized as norovirus infection alone, rotavirus infection alone, bacterial infection alone, co-infection, and negative samples.
RT-PCR, reverse transcription polymerase chain reaction; PCR, polymerase chain reaction.

Table 1. Performance of RDTs, stratified by age groups, for norovirus (QuickNavi™ – Norovirus2) and rotavirus (VIKIA® Rota-Adeno) including sensitivity, specificity, NPV, PPV and accuracy.

RDT	Age group	No. of samples	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy
QuickNavi™ - Noro	All	358	27.45 (28/74)	97.66 (250/256)	77.16 (250/324)	82.35 (28/34)	0.78
	Age <5 yr.	337	27.84 (27/97)	97.50 (234/240)	76.97 (234/304)	81.82 (27/33)	0.77
	Age >5 yr.	21	20.00 (1/5)	100.00 (16/16)	80.00 (16/20)	100.00 (1/1)	0.81
VIKIA® Rota-adeno	All	358	44.79 (43/96)	91.60 (240/262)	81.91 (240/293)	66.15 (43/65)	0.79
	Age <5 yr.	337	44.44 (40/90)	91.50 (226/247)	81.88 (226/276)	65.57 (40/61)	0.79
	Age >5 yr.	21	50.00 (3/6)	93.33 (14/15)	82.35 (14/17)	75.00 (3/4)	0.81

RDT, rapid diagnostic test; NPV, negative predictive values; PPV, positive predictive values.

Table 2. The positivity rate of norovirus genotypes detected by RDT for norovirus (QuickNavi™ – Norovirus2)

Norovirus genotypes	No. of samples	RDT for norovirus		
		Positive	Negative	Positivity rate (%)
Group I				
GI.3	2	0	2	0
GI.4 + GII.16	1	0	1	0
GI.5	1	0	1	0
Total Group I	4	0	4	0
Group II				
GI.5 + GII.4	2	2	0	100
GI.15 + GII.4	2	0	2	0
GII.2	2	0	2	0
GII.3	17	2	15	11.8
GII.4	41	20	21	48.8
GII.5	1	0	1	0
GII.6	1	0	1	0
GII.13	2	1	1	50
GII.14	1	1	0	100
GII.16	1	0	1	0
GII.17	11	0	11	0
GII.21	1	0	1	0
Total Group II	82	26	56	31.7
Not determined	16	2	14	12.5
Total	102	28	74	27.5

RDT, rapid diagnostic test.

norovirus and rotavirus has an accuracy of 0.78 and 0.79, respectively. This also improves if co-infection has been removed with 0.89 and 0.83 for norovirus and rotavirus diagnostic tests, respectively, as shown in **Table 1**.

3. False positive/cross-reactivity

False positive results of RDT for norovirus occurred in 6 samples, and 22 samples were found in RDT for rotavirus. Among them, false positives RDT for rotavirus were found to have cross-reactivity with 11 norovirus infections (7 cases of GII.4 and 4 cases of GII.17) and have 3 infected bacterial stools (*Salmonella* species, *Salmonella* group D, and *Escherichia coli*). On the contrary, 6 of the false positive RDTs for norovirus were found to have no cross-reactivity against rotavirus and bacterial infections as shown in **Table 3**.

DISCUSSION

The sample size of this study is considered to be one of the largest studies done in Thailand [20-22]. From 358 stool samples collected, the prevalence of norovirus and rotavirus is 28.5% (102) and 27% (96), respectively, with 6% (21) of norovirus and rotavirus co-

Table 3. False positive of RDTs for norovirus and rotavirus

RDTs	Causing organisms of false positive of RDTs
RDT for Rotavirus (N = 22)	Norovirus 11 cases
	Bacteria 3 cases (*e.g. Salmonella* species, *Salmonella* group D, and *Escherichia coli*)
	Negative 8 cases
RDT for Norovirus (N = 6)	Negative 6 cases

RDT, rapid diagnostic test.

infection. Compared to the recent systematic literature review of the role of norovirus in sporadic gastroenteritis worldwide from 1990 – 2008, we found that the pooled proportion of hospitalized norovirus infected patients is relatively lower compared to this study (11% [95% CI 8 - 14%]) [1]. On the contrary, rotavirus prevalence was found to be lower than the previous studies in Thailand ranging from 28 - 45% [23-25].

Compared to the previous norovirus diagnostic test studies, our research shows much lower sensitivity. We detected norovirus using Quick Navi-Noro 2 as RDT in this study because it is widely used in Thailand. The antibodies of Quick Navi-Noro2 are mouse's monoclonal antibodies which can detect both GI and GII norovirus strains with high sensitivity and specificity according to previous studies (sensitivity = 92 - 96.7%, specificity = 98.3 - 100%) and the manufacturer's manual (sensitivity = 92%, specificity = 98.3%) [5-7]. The result shows the specificity of 97.7%, which is quite similar. However, the sensitivity of Quick Navi-Noro 2 RDT is lower than previous studies, which are 27.5% *vs.* 92 - 96.7%. We hypothesize that these findings may result from several factors. Firstly, the quality of the samples, as real clinical samples can have a varying qualities in terms of contamination and concentration of the viral particles compared to some studies that used confirmed clinical stools samples to test the accuracy of the RDTs. From the total of 102 RT-PCR positive norovirus samples that the concentration exceeds 1.0×10^2 copies/PCR reaction tube, only 28 were positive by RDT. Previous studies have shown that a viral load of at least 4.6×10^6 - 3.5×10^7 copies/g was needed for RDT to be positive or even as high as 10^8 copies/g in GII.17 genotypes [26]. Although these clinical samples were collected in hospitalized patients that tend to have a higher concentration of the viral pathogens in the stool, there is no guarantee [27-29]. Secondly, Incidental RT-PCR positivity can lower the test sensitivity. These incidents are caused by chronic shedding, asymptomatic detection, and recent vaccination [30]. These patients tend to have lower viral load that could reduce the sensitivity of the test. Thirdly, co-infection can lower the sensitivity due to antigen-antibody interference or altering host immune response [31]. If we exclude co-infection from this analysis, the accuracy can increase up to 0.89 from 0.78. Further studies on the mechanism of co-infection on immune response and clinical outcomes might be considered. Lastly, other causes of diarrhea, including other viral, parasite infection, or other etiologies, can overlap with the diagnosis of acute gastroenteritis and could interfere with the accuracy analysis, especially in NPV and PPV results. Noted that in a subgroup analysis of norovirus genotypes, we found that the positive rate of GI norovirus is 0% compared with GII virus, which is 31.7%. We can imply that this RDT is more sensitive to GII strain, especially GII.4 which causes the majority of outbreaks that give a positive rate of 48.8%.

VIKIA® Rota-Adeno (BioMérieux, France) was stated to have high sensitivity (77 - 98.8%) and specificity (89 – 100.0%) [8-13]. The specificity of this study is similar at 91.6%, but for the sensitivity, the result was below those standards at 44.8%. A similar explanation may be implied in norovirus RDT. For rotavirus RDT, the minimal viral required for a positive test was 6.37×10^5 copies/g but even as high as 6.09×10^7 copies/g can still be found as false

negative [10]. Therefore, rotavirus is easier to detect than norovirus due to the threshold of the test. In real clinical samples, we found that the result of accuracy of the tests was lower than the standard from both previous studies and handouts. These results might be misguiding for healthcare providers in both clinical diagnoses and outbreak determination. Calibration of the RDT using a standard rotavirus sample, obtained from any of the rotavirus regional laboratories, might be essential before the applying the test [32].

Cross-reactivity is a phenomenon where different antigens from different organisms appear similar and react with the same immune system causing false positive results in the test. Several studies have claimed that both norovirus and rotavirus RDT have no cross-reactivity [5, 6, 10, 16-19]. Except one study that found cross-reactivity between norovirus RDT with rotavirus [18]. This research shows some potential cross-reactivity in rotavirus RDT. However, this study finds no cross-reactivity in Quick Navi-Noro 2 over rotavirus and bacteria. This finding is correlated with previous studies and Quick Navi-Noro 2's handout [5, 6]. On the contrary, VIKIA Rota-adeno had 22 false positive tests despite the specificity of 91.60%. Eleven out of 22 false positive tests (50%) were related to norovirus infection including GII.4 and GII.17 genotype. These findings were never mentioned before in the previous studies and VIKIA Rota-adeno's handout [10, 16, 19]. This finding suggests that we must carefully interpret rotavirus RDT positive cases which indeed are norovirus. We hypothesize that the variation of the norovirus antigen from protein VP1 might be the reason that this pathogen can cross-react to other antibodies. Still, it would be too early to conclude that cross-reactivity of the norovirus in rotavirus RDT was due to part of antigen or epitope that fit rotavirus monoclonal antibodies because no previous studies had determined the exact epitope and paratope of monoclonal antibody in both norovirus and rotavirus RDTs. There is some available information about antibodies against rotavirus specific epitope, but most of them were part of the clinical immune response of host to the virus but not in the RDT. Finding the exact epitope from the virus or paratope of the antibody might help develop a new RDT with more accuracy. Also, further study of other rotavirus RDTs may help to determine the cross-reactivity and common epitope that share the same characteristic to norovirus.

The diagnosis of acute gastroenteritis was made based on different physicians' opinion where interrater variability can happen. The demographic data of this study's participants is not available in order to determine the effect of some factors (such as chronic infection, vaccination status) on the accuracy of the test. The research was done in only hospitalized patients which did not represent the actual accuracy of the test in all types of patients. We didn't collect the data of the viral concentration in every positive specimen in order to prove the hypothesis that low sensitivity was caused by low viral load in stools. Finally, the data of other enteric pathogens in the samples is not available because this study focused mainly on norovirus, rotavirus, and bacterial infection, which are responsible for the majority of acute gastroenteritis cases with identified etiology [33].

In clinical specimens, RDTs for both rotavirus and norovirus have high specificity but low sensitivity. The cross-reactivity found in rotavirus RDT is not uncommon. In positive rotavirus RDT, there are chances that it might be norovirus. The interpretation of these tests should be carefully considered.

ACKNOWLEDGEMENT

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Two-by-two table showing the result of norovirus testing in all samples

Click here to view

Supplementary Table 2
Two-by-two table showing the result of norovirus testing in samples age <5 years old

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Supplementary Table 3
Two-by-two table showing the result of norovirus testing in samples age >5 years old

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Supplementary Table 4
Two-by-two table showing the result of rotavirus testing in all samples

Click here to view

Supplementary Table 5
Two-by-two table showing the result of rotavirus testing in samples age <5 years old

Click here to view

Supplementary Table 6
Two-by-two table showing the result of rotavirus testing in samples age <5 years old

Click here to view

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