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Comparison of allergen responses based on the TRUE Test and IQ Chamber system in Korean patients

Background: A comparison between responses to allergens based on the TRUE Test® (TT) and IQ® Chamber (IQC) in Europeans has been previously reported, however, no such study has been performed in Asians. **Objectives:** To compare allergen responses using the TT and IQC (using the Korean standard series) in order to gather more information regarding the positive response rates for each allergen and the clinical value of IQC. **Materials & methods:** Suspected contact dermatitis patients were enrolled and tested with 18 allergens using the TT and IQC. **Results:** The test was performed in 214 patients. Simultaneous positive results for both tests were recorded in 242 cases (positive concordance rate: 66.7%). IQC yielded more positive results. Allergens with a high positive concordance rate were nickel sulphate (82.1%), thimerosal (78.6%), and *p*-phenylenediamine (73.3%). IQC mostly showed similar or higher positive rates than TT, with high concordance. **Conclusions:** We recommend the IQC method as a screening test in patients with suspected contact dermatitis. To compensate for possible false positive results, careful history taking and a different patch test should be performed when appropriate.

Key words: concordance, IQ® Chamber, Korean standard series, patch test, TRUE Test®

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The patch test is the most effective diagnostic method for contact dermatitis, and is performed worldwide in many different forms [1, 2]. Efforts to standardise patch tests are controversial, and this is associated with a number of methodological and interpretative prob-

lems. However, many studies have demonstrated the clinical value and reproducibility of the investigator-loaded Finn Chamber (FC) [3, 4] system and manufacturer-loaded test systems, such as Epiguick [5] and TRUE test (TT) [6]. The reproducibility of the FC varies among reports, but is

Table 1. Comparison of allergens using the KSS and TT panels.

Allergen from the KSS panel (for IQC)	Concentration (% w/w)	Allergen from the TT panel	Concentration ($\mu\text{g}/\text{cm}^2$)
Nickel (II) sulphate hexahydrate	5.0% pet	Nickel sulphate	200
Lanolin alcohol (wool alcohol)	30.0% pet	Wool alcohols	1000
Neomycin sulphate	20.0% pet	Neomycin sulphate	230
potassium dichromate	0.5% pet	Potassium dischromate	23
Fragrance mix I	8.0% pet	Fragrance mix	430
Colophonium	1.0% pet	Colophonium	850
Myroxylonpereiarae resin (Balsam Peru)	1.0% pet	Balsam of Peru	800
Cobalt(II) chloride hexahydrate	1.0% pet	Cobalt chloride	20
4-Tetra-butylphenol formaldehyde resin	1.0% pet	<i>p</i> -Tert-butylphenol formaldehyde resin	50
Paraben mix	16.0% pet	Paraben mix	1000
Methylosithiazolinone+ methylchloroisithiazolinone	0.01% aq	Cl+Me-isothiazolinone	4
Quaternium-15	1.0% pet	Quaternium-15	100
2-Mercaptobenzothiazole (MBT)	2.0% pet	Mercaptobenzothiazole	75
<i>p</i> -Phenylenediamine (PPD)	1.0% pet	<i>p</i> -Phenylenediamine	90
Formaldehyde	1.0% pet	Formaldehyde	180
Mercapto mix	2.0% pet	Mercapto mix	75
Thimerosal	0.1% pet	Thimerosal	8
Thiuram mix	1.0% pet	Thiuram mix	25

aq: aqua; IQC: IQ Chamber; KSS: Korean Standard Series; pet: petrolatum; TT: TRUE Test.

estimated at 70-95% [7]. Meanwhile, the reproducibility of the TT is approximately 95% [6]. The concordance between the two tests is reported to be 63-78% [8].

The IQ Chamber (IQC) system is an investigator-loaded method, and its strength lies in the fact that it is pre-loadable and does not involve physical stimulation (which can trigger metal allergies). In a previous study, Lazarov *et al.* argued that while allergen responses reported by the TT and IQC methods are highly concordant, the IQC is more sensitive to some allergens, particularly to those that are not identified by the TT [9]. The study by Lazarov *et al.* is the only study to compare the TT and IQC, and included only European participants. To date, no similar study has been conducted in an Asian cohort.

With the above in mind, the aim of this study was to compare allergen responses yielded by the TT and IQC (with the Korean standard series [KSS]) to measure the differences in the rates of positive response between the tests and to assess the clinical value of the IQC in the Korean population.

Methods

This was a multicentre study, conducted in 14 centres, including Hallym Sacred Heart Hospital. Patients who visited any of the included centres from September 2015 to April 2016 were enrolled. Patients were included if they were clinically suspected to have allergic contact dermatitis, were 18-65 years old, and were suspected to have experienced allergic contact dermatitis based on their past medical history (even if no clinical symptoms were present during the visit to their healthcare institution). We excluded patients who had significant infections, had been diagnosed

with cancer, were difficult to follow and/or monitor, were pregnant or lactating, or were otherwise determined unable to participate based on the investigator's opinion. Every eligible person provided informed consent and underwent a patch test using both the TT and IQC methods (using the KSS). The study protocol (No. 2015-I033) was approved by the institutional review board/ethics committee of Hallym University Sacred Heart Hospital.

The participants completed questionnaires designed to collect basic information, including present and past medical history and whether they had ever received a patch test prior to participation in the study. In this study, 18 allergens common to the KSS (25 allergens) and TT (24 allergens) were selected (*table 1*). The devices for the TT and IQC were placed on the left and right of the lesion-free upper back, respectively, and occluded appropriately. Each was then removed at Day 2 and evaluated 30 minutes later, and again at Day 4 [10]. All results were recorded photographically and categorized according to the criteria proposed by the International Contact Dermatitis Research Group. According to these criteria, a doubtful reaction (+/-) refers to homogenous erythema without infiltration, a weak positive reaction (+1) to erythematous papules and infiltration, a strong positive reaction (+2) to lesions with discrete vesicles, and an extreme positive reaction (+3) to lesions with coalescing vesicles and bullous or ulcerative reactions. Furthermore, we defined a positive result as either weak positive (+1) or a stronger reaction [10]. For both methods, allergens were placed at approximately the midline of the back [6, 11, 12]. Positive concordance was defined when both systems reported a positive reaction for the same allergen, and the formulae described by Lazarov *et al.* were used for the analysis (*table 2*) [9]. In contrast, discordance was defined when one system reported a positive reaction but

Table 2. Formulas used to calculate positive concordance.

% positive concordance =	$\frac{\text{concordant positive allergens (IQC, TT)} \times 2}{\text{total positive allergens (IQC)} + \text{total positive allergens (TT)}} \times 100$
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IQC: IQ Chamber using the Korean Standard Series allergens; TT: TRUE test.

Table 3. Comparative results for allergens tested using the IQC (with KSS allergens) and TT.

Allergen	Positive tests			% concordance	Discordance on IQC	Discordance on TT	κ
	IQC	TT	IQC+TT				
Nickel sulphate	61	51	46	82.1	15	5	0.76
Wool alcohols	2	7	2	44.4	0	5	0.44
Neomycin sulphate	5	3	1	25.0	4	2	0.24
Potassium dischromate	19	10	9	62.1	10	1	0.6
Fragrance mix	20	11	8	51.6	12	3	0.48
Colophonium	4	2	1	33.3	3	1	0.32
Balsam of Peru	9	4	3	46.2	6	1	0.45
Cobalt chloride	37	18	15	54.5	22	3	0.49
<i>p</i> -Tert-butylphenol formaldehyde resin	11	10	7	66.7	4	3	0.65
Paraben mix	1	1	1	100.0	0	0	1
Cl+ Me-isothiazolinone	3	4	3	85.7	0	1	0.85
Quaternium 15	1	0	0	0.0	1	0	0
Mercaptobenzothiazole	0	0	0	0.0	0	0	0
<i>p</i> -Phenylenediamine	16	14	11	73.3	5	3	0.71
Formaldehyde	2	1	1	66.7	1	0	0.66
Mercapto mix	1	2	1	66.7	0	1	0.66
Thimerosal	13	15	11	78.6	2	4	0.77
Thiuram mix	2	3	1	40.0	1	2	0.39
Total	207	156	121	66.7	86	35	0.65

KSS: Korean Standard Series; IQC: IQ Chamber; TT: TRUE test; κ : Cohen's kappa.

the other reported a negative reaction for a specific allergen [9].

All statistical analyses were performed using IBM SPSS version 22.0 for Windows. We used Cohen's kappa coefficient (κ) as a statistical index for inter-rater agreement for qualitative categorical items. Although there is no universally accepted guideline, we characterized the magnitude of κ -value as follows, according to previous reports: <0 = "no agreement", $0-0.20$ = "slight agreement", $0.21-0.40$ = "fair agreement", $0.41-0.60$ = "moderate agreement", $0.61-0.80$ = "substantial agreement", and $0.81-1$ = "almost perfect agreement".

Results

This was a multicentre study involving 14 centres and 214 patients (68 men and 146 women). The mean age was 41.6 years, and the mean onset of disease occurred eight months before the first visit. Approximately 10% of the study population had atopic dermatitis, allergic rhinitis, or asthma.

A total of 10,486 individual patch test results were gathered, and the results of the 18 pre-selected allergens were compared (7,704 tests). A total of 363 positive reactions were observed, representing 4.7% of the total test sample; 207 results were obtained using the IQC system while 156 were obtained using the TT panel. A total of 242 tests (121 pairs) were positive in both groups, and the positive concordance rate was 66.7% (calculated according to the formula: $121 \times 2 / [207 + 156] \times 100$).

Comparisons of the test results for each allergen are shown in table 3. The allergens with high concordance were nickel sulphate (82.1%), thimerosal (78.6%), and *p*-phenylenediamine (PPD) (73.3%). The moderate concordance group included *p*-tert-butylphenol formaldehyde resin (66.7%), potassium dischromate (62.1%), cobalt chloride (54.5%), and fragrance mix (51.6%). The low concordance group included Balsam of Peru (46.2%), wool alcohols (44.4%), and neomycin sulphate (25.0%). Paraben mix, formaldehyde, mercapto mix, and Cl+Me-isothiazolinone yielded positive results in some patients, but the numbers were too small to allow statistical analysis. The total κ -value was 0.65, which indicated substantial

Table 4. Comparison of intensity levels of the corresponding allergic reactions.

Allergen	(+1)		(+2)		(+3)	
	IQC	TT	IQC	TT	IQC	TT
Nickel sulphate	27	26	17	19	2	1
Wool alcohols	2	2				
Neomycin sulphate	1	1				
Potassium dischromate	7	6	2	3		
Fragrance mix	6	6	2	1		1
Colophonium		1	1			
Balsam of Peru	2	1	1	2		
Cobalt chloride	12	14	3	1		
<i>p</i> -Tert-butylphenol formaldehyde resin	7	6	0	1		
Paraben mix	1			1		
Cl+ Me-isothiazolinone	2	2	1	1		
<i>p</i> -Phenylenediamine	6	8	4	2	1	1
Formaldehyde	1	1				
Mercapto mix	1			1		
Thimerosal	9	8	1	2	1	1
Thiuram mix	1	1				
Total	85	83	32	34	4	4

IQC: IQ Chamber using the KSS; TT: TRUE Test.

agreement between the two raters. The κ -values were approximately equal to percent concordance, and the allergens with high concordance (nickel sulphate, thimerosal, and *p*-phenylenediamine) showed κ -values >0.7 , confirming a high degree of agreement.

Table 4 summarizes the comparisons of the intensity levels of corresponding allergic reactions between both tests. Concordance of reaction strength was 88.4%. The greatest percent of discordance of intensity level of response among allergens was for nickel sulfate, cobalt chloride, and *p*-phenylenediamine, but the differences were not so significant. No paired reactions showed an intensity difference >1 .

Discussion

Contact dermatitis is diagnosed by examining a patient's history and the location and progression of his/her lesions. Although it is possible to presume the exact cause using this information alone, a patch test is the most effective method to confirm the diagnosis [10]. When performing patch tests, it is crucial that the results are read accurately, and positive results should be correlated with clinical findings [10, 13]. The reproducibility of a test is an indicator of its credibility and value as a diagnostic method. Several factors can affect the accuracy of a test, including the different vehicles and concentrations of allergens used, the amount of material applied, and the interpretation of responses [6]. Furthermore, while the patch is in place, the patient must avoid showering, exercising, or performing any work that might induce sweating in order to prevent the dilution of allergens

by water or sweat. For this reason, we avoided the summer months during the study period.

For the TT, 24 types of dried, quantified allergens are utilised, which are adhered to the patch. The patches can be stored at low temperatures for approximately two years. The positive response rate of the TT is approximately 63~78% [11, 14, 15]. The TT is a manufacturer-loaded system, making it easy and simple to use. Furthermore, the amount of allergen used is only 10~50% of that used by the FC, and the method provides good reproducibility [6]. The fact that the TT is used globally may allow comparative analyses of positive rates among nations or races. The negatives of the TT are its high cost and the fact that the available allergens are limited, which makes it difficult to use the TT for a new suspected allergen. Finally, the results of the TT cannot be completely trusted in cases in which the patient has showered or sweated, as the patch is hydrophilic and holds a relatively low amount of allergen, as mentioned above. The IQC system is composed of a polyethylene plastic chamber and hypoallergenic tape, solving the issues of metal allergy induction and physical stimulation associated with the FC. Furthermore, it is an investigator-loaded system, and can be preloaded and refrigerated. However, because the system must be prepared by the investigator, it is associated with long preparation times. Furthermore, a small number of studies concerning the validity of the IQC have discouraged its use.

The most widely used patch tests in clinical practice are the IQC, TT, and FC. There are some controversies regarding the standardisation of patch tests, and many studies have assessed the positive rates and reproducibility for various allergens of each test [6, 9]. FC results show reproducibility of approximately 70~90%, while those of the TT show reproducibility of 95%. The positive reaction

concordance rate between the FC and TT is estimated at 63~78% [9]. Goh argued that the overall concordance between the TT and FC is 64%, and that positive reactions for PPD and neomycin are more frequent with the FC [16]. Suneja *et al.* found that when detecting clinically relevant allergens, the FC was more sensitive to fragrance mix, Balsam of Peru, and thiuram mix, while the TT was more sensitive to nickel, neomycin, and methylchloroisothiazolinone/methylisothiazolinone(MCI/MI) [15]. These previous findings suggest that while the methods may be comparable, each test has its own rates of false positives and negatives and sensitivities to different allergens. It is therefore necessary to perform another test for allergens that yield a positive response with the first method.

The IQC has been studied less intensively than either the TT or FC [9, 11]. One study that compared the IQC and FC for the assessment of 10 common allergens reported good agreement, with some variability among responses [11]. Lazarov *et al.* reported a positive concordance between the TT and IQC of 64.4%, and the allergens with the highest degree of concordance were MCI/MI (81.5%), nickel sulphate (79%), formaldehyde (76.9%), and PPD (72.7%) [9]. Analysis of positive reactions to allergen exposure demonstrated that some allergens with low to moderate concordance, such as cobalt or Balsam of Peru, were associated with high positive detection rates by IQC [9].

Unlike previous studies, we used the IQC system in combination with the KSS rather than the European standard series. We compared the results of the IQC/KSS to those of the TT panel and observed a positive concordance rate of 66.7%, which was similar to previous results. The allergens with higher positive rates were identical in both tests, although the exact rates and their order were slightly different between the methods. The concordance of reaction strength among all cases was 88.4%, and the differences in reactions between the tests, if present, were all $\leq +1$ (in line with previous results). The IQC showed similar or stronger positive reaction rates except in the case of a few allergens. Allergens that showed moderate concordance (51.6-62.1%), such as fragrance mix, potassium dichromate, and cobalt chloride, showed more positive results for IQC than for TT, and this result is similar to that of Lazarov *et al.* [9]. In particular, allergens that showed positive results, which were more than twice as strong for IQC than for TT (Balsam of Peru and cobalt chloride), were demonstrated to show large differences in positive results based on previous studies [9]. Furthermore, a number of previous studies demonstrated that allergens related to scent, such as fragrance mix and Balsam of Peru, show higher positive rates based on the FC methodology than on the TT, and similar results were reported by studies comparing IQC and TT, including this study [6, 9, 15-17]. Meanwhile, allergens, such as wool alcohol, showed higher positive rates based on the TT compared to the IQC, with a relatively small number of positive results, but with a significant difference (concordance: 44.4%). Wool alcohol, which is commonly used in the production of cosmetics, did not yield more positive results based on the TT, compared to the FC, or any significant differences relative to previous studies [14, 15]. In contrast, quaternium-15 has been reported to have higher positive rates based on the TT than on the FC or IQC [9, 14], but we observed only a few positive results in this study.

This study was limited in a number of ways. First, it was not blinded or randomised, and statistically significant analysis was not possible for some allergens due to the small number of cases included. Moreover, we used questionnaires to correlate demonstrated exposure with disease, however, not enough replies were received. The replies were often too ambiguous to be put to practical use, and the questionnaire was therefore not useful for obtaining information regarding clinically relevant allergen exposure.

In conclusion, high positive response rates for allergens using the IQC method can compensate for false negative results obtained via the TT. This finding justifies the use of the IQC as a screening test, and we suggest that the IQC could be used for initial diagnosis in patients with suspected contact dermatitis because it shows higher positive rates than the TT. However, because false positivity cannot be ruled out, findings should be compared to medical history. If the findings do not match the patch test results, a different type of patch test that provides a high positive rate for the allergen in question should be performed. ■

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