

Evaluation of antibody screening and identification pre-transfusion tests using DG Gel cards

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Abstract

Background

Pre-transfusion tests vary in sensitivity and specificity and should be evaluated before their implementation into routine use. The aim of this study was to evaluate the diagnostic accuracy of the Grifols DG Gel column agglutination system and to compare the data with two other column agglutination systems used in our laboratory: Ortho BioVue and Bio-Rad. Special attention was focused on using more vials of reagent red blood cells by Grifols DG Gel system when compared to other systems in order to investigate whether it increases the sensitivity for clinically significant antibodies.

Methods

All samples were tested in parallel with Grifols DG Gel, Ortho BioVue and Bio-Rad cards according to manufactures' instructions. Samples were processed through manual instrumentation. Tests were performed by trained and experienced staff. A total of 419 tests were performed on 302 samples.

Results

Concordant results between Grifols DG Gel system and the other two systems were obtained in 93.8% of the tests. For antibody screening by Grifols DG Gel system, sensitivity was 97.53%, specificity was 100%, predictive positive value was 100% and predictive negative value was 97.73%. For antibody identification, the accuracy was 96.03% for Grifols DG Gel system, 97.22% for Ortho BioVue and 94.44% for Bio-Rad.

Conclusions

The Grifols DG gel system shows high diagnostic accuracy and is safe for pre-transfusion compatibility procedures in blood transfusion laboratories. Using more vials of reagent red blood cells by Grifols DG Gel system when compared to other systems increases the sensitivity for some antibody specificities, particularly anti-Jk^a. This could have major impact on the prevention of delayed transfusion reactions.

Keywords: program evaluation, blood grouping and crossmatching, haemagglutination tests, erythrocytes, isoantibodies

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1. Introduction

The demands of blood transfusion laboratories are growing, especially in the aspect of patient safety, performance and cost-effectiveness. For the purpose of rationalisation of pre-transfusion testing protocols, a method in which antibody screening determines the presence of only clinically significant antibodies is preferred in blood transfusion laboratories¹. Published comparisons of antibody detection methods (conventional tube, solid-phase, column agglutination) has shown variations in methods' sensitivity and specificity²⁻⁵. Clinically insignificant antibodies may be detected at a higher rate, particularly if methods are more sensitive. Understanding the strengths and limitations of validated methods used can optimize antibody detection⁶.

Column agglutination technology (CAT) that uses a gel or a glass beads matrix in microtubes for the agglutination detection has been successfully applied for over 25 years⁷. The well-known advantages of CAT over the tube technology are: the washing step in the anti-globulin phase is omitted resulting in the faster performance, the reaction in the column is stable facilitating interpretation of the weak reactions and enabling reading reactions repeatedly, and there is also the possibility of automation which decreases human errors and provides the traceability of the results⁸.

Grifols DG Gel (Diagnostic Grifols S.A., Barcelona, Spain) is a new column agglutination system on the Croatian market for pre-transfusion testing. The Grifols DG Gel system can be used in manual techniques or through full automation instrumentation with a small capacity Wadiana analyser, a medium capacity Erytra Eflexis analyser, which is a new analyser on the market, or with a high throughput high capacity Erytra analyser (Diagnostics Grifols, S.A. Barcelona, Spain).

Before implementing the new system into routine use, an evaluation to confirm sensitivity and specificity of the system should be done. Major advantage of the Grifols DG Gel system is an 8-column gel card, which allows more flexibility in choosing reagent RBCs for antibody screening and antibody identification with more examples of phenotypes expressing and lacking the corresponding antigen when compared to 6-column cards. Using more vials of reagent red blood cells (RBCs) for antibody screening and antibody identification enhances double-dose expression of clinically relevant

antigens⁹, which is particularly important for the prevention of delayed transfusion reactions¹⁰.

The aim of this study was to evaluate the performance of the Grifols DG Gel system for antibody screening and antibody identification through manual instrumentation [Grifols DG Therm and Grifols DG Spin (Diagnostics Grifols, S.A. Barcelona, Spain)], with a special focus on using more vials of reagent RBCs when compared to those used with other systems in our laboratory in order to investigate whether it increases the sensitivity for clinically significant antibodies.

2. Methods

2.1. Study design

Study was conducted at the Department of Transfusion Medicine of the Clinical Department of Transfusion Medicine and Transplantation Biology, University Clinical Hospital Zagreb from January to July 2016. A total of 419 tests were performed on 302 samples: 167 antibody screenings on 167 samples and 252 antibody identification panels on 135 samples.

For antibody screening 86 patient samples of whole blood collected in ethylenediaminetetraacetic acid within 24 hours from sampling and 81 plasma samples containing antibodies of known specificity were used. Of the 81 samples with antibodies of known specificity, there were 57 samples with one antibody specificity, 20 samples with two antibody specificities and 4 samples with three antibody specificities; in total 109 antibody specificities.

For antibody identification 135 plasma samples containing antibodies of known specificity were used. Of these, there were 103 samples with one antibody specificity, 29 samples with two antibody specificities and 3 samples with three antibody specificities; in total 170 antibody specificities.

Plasma samples containing antibodies of known specificity had been stored at -30 °C and were thawed immediately before testing.

2.2. Materials

For the Grifols DG Gel card reagent RBCs 0.8% Serascan Diana 4 (four cells) were used for antibody screening,

while 0.8% Identisera Diana and Identisera Diana P (1-11 cells) together with Identisera Diana Extend and Identisera Diana Extend P (12-15 cells) were used for antibody identification. For the indirect anti-globulin (IAT) test and the enzyme test, DG Gel Coombs and DG Gel Neutral cards were used, respectively.

The Ortho BioVue card used reagent RBCs 0.8% Surgiscreen (three cells) for antibody screening and 0.8% Ortho Resolve Panel C (1-11 treated and untreated cells) for antibody identification. For the IAT test and the enzyme test anti-human globulin anti-IgG; -C3d polyspecific and Neutral cards were used, respectively.

For the Bio-Rad card reagent RBCs ID-DiaCell I-II (two cells) were used for antibody screening, while ID-DiaPanel and ID-DiaPanel-P (1-11 cells) were used for antibody identification. For the IAT and the enzyme test ID-LISS/Coombs and NaCl, Enzyme test and Cold Agglutinins cards were used, respectively.

Both IAT and the enzyme test were performed for antibody identification.

2.3. Methods

All samples were tested in parallel with Grifols DG Gel, Ortho BioVue (Ortho-Clinical Diagnostics, Inc., Raritan, NJ, USA) and Bio-Rad cards (Bio-Rad Laboratories, Inc., CA, USA) according to manufactures' instructions. Samples were processed through manual instrumentation (Grifols DG Therm and Grifols DG Spin in case of the DG Gel System; Ortho BioVue System Heat Block and Ortho BioVue System for Ortho BioVue cards; Bio-Rad ID-cards were processed through manual instrumentation in the Bio-Rad Gel Test ID-Micro Typing system). Tests were performed by trained and experienced staff.

For the Grifols DG Gel system, the technique consisted of pipetting 50 μ L of reagent RBCs and 25 μ L of plasma in the microtube, 15 minutes of incubation and 9 minutes of centrifugation.

For the Ortho BioVue system, the technique consisted of pipetting 50 μ L of reagent RBCs and 40 μ L of plasma in the microtube, 15 minutes of incubation and 5 minutes of centrifugation.

For the Bio-Rad system, the technique consisted of pipetting 50 μ L of reagent RBCs and 25 μ L of plasma in the microtube, 15 minutes of incubation and 10 minutes of centrifugation.

2.4. Interpretation of results

A positive reaction is agglutination seen if RBCs are retained in the column. A negative reaction is absence of agglutination seen if packed RBCs are fallen at the bottom of the column. In antibody screening the reactivity of the serum as whole was evaluated in cases of multiple antibodies, regardless of whether one or all antibodies present were observed to be positive.

Antibody identification was performed according to the British Committee for Standards in Haematology (BSCH) (10). The presence of additional antibodies was excluded.

The result was considered to be false positive when a positive result did not correlate with antibody specificity. The result was considered to be a false negative when the result with samples containing antibodies of known specificity was negative. All discrepancies were resolved.

2.5. Statistical analysis

The results were processed by statistical software SPSS 25. Descriptive statistics was used in the statistical analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the accuracy of CAT systems were calculated according to standard formulae including the 95% confidence intervals (CI)¹¹.

3. Results

Concordant results between Grifols DG Gel and other two systems were observed for 393 of the 419 (93.8%) tests. Antibody specificities of the samples for antibody screening and identification are shown in Table 1.

3.1. Antibody screening

Of the 167 samples with antibody screening performed, discordant results were observed in 3 (1.8%) samples (Table 2). All discordant results were false negative: 2 in Grifols DG Gel (anti-M and -K) and 1 in Bio-Rad (anti-E). The results of the antibody screening test with estimated sensitivity, specificity, PPV, NPV and the accuracy of the compared systems are shown in Table 3.

Table 1. Antibody specificities of the samples for antibody screening and identification

Antibody specificity	Samples for antibody screening			Samples for antibody identification		
	Single antibody	Multiple antibody	Total number of antibodies N (%)	Single antibody	Multiple antibody	Total number of antibodies N (%)
anti-C	0	13	13 (11.9)	2	14	16 (9.4)
anti-c	4	3	7 (6.4)	2	6	8 (4.7)
anti-C ^w	0	1	1 (0.9)	0	2	2 (1.2)
anti-D	16	12	28 (25.7)	28	14	42 (24.7)
anti-E	6	11	17 (15.6)	19	10	29 (17.1)
anti-Fy ^a	1	1	2 (1.8)	3	1	4 (2.4)
anti-Fy ^b	1	0	1 (0.9)	1	0	1 (0.6)
anti-G	0	1	1 (0.9)	0	1	1 (0.6)
anti-Jk ^a	0	1	1 (0.9)	5	1	6 (3.5)
anti-K	13	5	18 (16.5)	20	10	30 (17.6)
anti-k	1	0	1 (0.9)	-	-	-
anti-Kp ^a	0	1	1 (0.9)	1	2	3 (1.7)
anti-Le ^a	4	2	6 (5.5)	5	3	8 (4.7)
anti-Lu ^a	0	1	1 (0.9)	4	0	4 (2.4)
anti-M	10	0	10 (9.2)	12	2	14 (8.2)
anti-P ₁	-	-	-	0	1	1 (0,6)
anti-S	1	0	1 (0.9)	1	0	1 (0.6)
Σ	57	52	109 (100)	103	67	170 (100)

Table 2. Samples with discordant results in the antibody screening test

Antibody specificity	DG Gel	Ortho BioVue	Bio-Rad
anti-E	Positive	Positive	Negative
anti-K	Negative	Positive	Positive
anti-M	Negative	Positive	Positive

Table 3. Diagnostic accuracy of antibody screening test for compared systems

	Grifols DG Gel	Ortho BioVue	Bio-Rad
True positive	79	81	80
False positive	0	0	0
True negative	86	86	86
False negative	2	0	1
Sensitivity (95% CI)	97.53 (91.36-99.70)	100 (99.55-100)	98.77 (93.31-99.97)
Specificity (95% CI)	100 (95,80-100)	100 (95.80-100)	100 (95.80-100)
PPV (95% CI)	100	100	100
PNV (95% CI)	97.73 (91.63-99.41)	100	98.85 (92.46-99.83)
Accuracy (95% CI)	98.80 (95.74-99.85)	100 (97.82-100)	99.40 (96.71-99.98)

3.2. Antibody identification

A total of 252 tests for antibody identification were performed on 135 samples. Discordant results were observed in 23 (9.1%) tests, including IAT and the enzyme test (the antibody was detected with one or two systems). Table 4. shows the list of identified antibodies and antibodies with discrepancies between Grifols DG Gel, Ortho BioVue and Bio-Rad systems. There were

no samples with nonspecific results and no sample was identified as a prophylactic anti-D antibody.

Of the 23 discrepancies, Grifols DG Gel system detected the antibody on 13 occasions (242 identified out of 252; accuracy of 96.03%), Ortho BioVue on 16 occasions (245 identified out of 252; accuracy of 97.22%) and Bio-Rad on 9 occasions (238 identified out of 252; accuracy of 94.44%).

Table 4. **Antibody identification test (n = 252 in 135 samples)**

Specificity	Total detected	Discrepancies in the test							
		Discor- dant cases	IAT			Discor- dant cases	Enzyme		
			Cases of identified antibodies				Cases of identified antibodies		
			Grifols DG Gel	Ortho BioVue	Bio- Rad		Grifols DG Gel	Ortho BioVue	Bio-Rad
anti-C	2					1	1		1
anti-C+D	9								
anti-C+E	1								
anti-C+G	1								
anti-C+D+Le ^a	2								
anti-C+D+Jk ^a	1								
anti-c	2								
anti-c+E	5					1	1 (-c)	1 (-c)	
anti-c+Fy ^a	1								
anti-C ^w +K	2					1	1 (-C ^w)	1 (-C ^w)	
anti-D	28	1		1	1				
anti-D+K	2								
anti-E	19	2	1	2	1				
anti-E+K	4					2	2 (-E)	2 (-E)	
anti-Fy ^a	3								
anti-Fy ^b	1								
anti-Jk ^a	5					1	1		
anti-K	20	1	1	1		1		1	1
anti-K+Kp ^a	2								
anti-Kp ^a	1					1			1
anti-Le ^a	5	5	2	5	1				
anti-Le ^a +M	1					1			1 (Le ^a)
anti-Lu ^a	4	2	1		1	1	1		
anti-M	12	2	1	2	1				
anti-M+P ₁	1								
Anti-S	1								
Total	135	13	6	11	5	10	7	5	4

There were 13 discrepancies between Grifols DG Gel, Ortho BioVue and Bio-Rad systems in the IAT test. These included 6 antibodies identified using the Grifols DG Gel system (single examples of anti-E, -K, -Lu^a, and -M and 2 examples of anti-Le^a), 11 antibodies identified using Ortho BioVue (single examples of anti-D and -K, 2 examples of anti-E and -M and 5 examples of anti-Le^a) and 5 antibodies identified using Bio-Rad (single examples of anti-D, -E, -Le^a, -Lu^a, and -M).

In the enzyme test, 10 discrepancies were identified; 7 antibodies were identified using the DG Gel system (single examples of anti-C, -c, -C^w, -Jk^a and -Lu^a and 2 examples of anti-E), 5 antibodies were identified using Ortho BioVue (single examples of anti-c, -C^w, -K and 2 examples of anti-E) and 4 antibodies were identified using Bio-Rad (single examples of anti-C, -K, -Kp^a and -Le^a).

4. Discussion

Overall, concordant results between Grifols DG Gel and the other two systems were observed for 393 tests: 164 of 167 (98.2%) screening tests and 229 of 252 (90.9%) antibody identification tests.

For antibody screening, only 1.8% cases were discordant (anti-E, -K and -M) and they were all detected by Ortho BioVue; two cases were detected by Bio-Rad (anti-K and -M) and one case (anti-E) was detected by Grifols DG Gel. Sensitivity and specificity for Grifols DG Gel were 97.53% and 100%, respectively. In comparison to the other two systems, Grifols DG Gel presented a lower sensitivity, while specificity was equal for all systems. In a study by Cid et al.¹², 100% of sensitivity and specificity were observed for Grifols DG Gel, which presented a higher sensitivity when compared to the Bio-Rad system and a higher specificity when compared to Ortho BioVue. In another study by Taylor et al.¹³, sensitivity and specificity for Grifols DG Gel were 90.63% and 99.94%, respectively.

Regarding antibody identification, Ortho BioVue had a higher diagnostic accuracy (97.22%) than both Grifols DG Gel and Bio-Rad (96.03% and 94.44%, respectively). The rates observed in this study for both Grifols DG Gel and Bio-Rad were a little lower than those observed by Taylor et al.¹³ (96.95% and 95.29%, respectively). Also, Chang et al.¹⁴ showed a higher accuracy (100%) for the antibody

identification tests on Erytra. Out of all discordant cases of antibodies in the IAT test, there were 2 examples of anti-M, which is a clinically significant antibody only if detectable at 37 °C, 2 examples of anti-Lu^a and 5 examples of anti-Le^a, which are clinically benign antibodies, while others were clinically significant antibodies (1 anti-D, 1 anti-K and 2 anti-E). Of discordant cases of antibodies in the enzyme test, there were 7 cases of clinically significant antibodies. Considering that 4 of these antibodies (1 anti-C, 1 anti-c, 2 anti-E) were detected only with enzyme-treated cells, their clinical significance remains controversial¹⁵. It is generally accepted, that it is not possible to detect all potentially clinically significant antibodies, nor to avoid all clinically insignificant antibodies⁶. Three or more positive results were missed by each system for different antibody specificities in antibody identification tests: Grifols DG Gel (1 anti-c, 1 anti-D, 1 anti-E, 1 anti-K, 3 anti-M and 4 anti-Le^a), Ortho BioVue (1 anti-S and 2 anti-Jk^a) and Bio-Rad (1 anti-c, 1 anti-K, 1 anti-Le^a, 1 anti-P₁, 2 anti-Jk^a and 3 anti-M). This benefits the Grifols DG Gel system for anti-Jk^a and -S, Ortho BioVue for anti-D, -E, -K, -Le^a, -M and -P₁ and Bio-Rad for anti-D and -S antibody specificities. However, one must be aware of the small sample size, particularly for some antibody specificities in this study.

Using more vials of reagent RBCs for antibody screening and antibody identification test by Grifols DG Gel system compared to those used by other two systems resulted in enhanced double-dose expression of clinically relevant antigens (C, c, E, e, Jk^a, Jk^b, Fy^a, Fy^b, M, N and S) and in higher sensitivity of Grifols DG Gel, particularly for anti-Jk^a antibody specificities. However, small sample size is the limitation of this study and for definite conclusions a bigger sample size is needed. Differences in the expression of rare antigens on the screening cells (Lu^a on BioRad, C^w and Kp^a on Grifols DG Gel and Ortho BioVue) did not influence antibody detection results, as antibodies to rare antigens were no single antibodies. Being rarely of clinical significance, Lu^a(+), Kp^a(+) and C^w(+) antigens are not essential on screening cells¹⁰.

In this study, procedures were set up to follow manufactures' instructions, therefore when analysing results different RBC suspension media (LISS), incubation time and centrifugation setting for each system should be taken into consideration. The conductivity of different low-ionic-strength solutions (LISS) calculated by Cid et al.¹², shown greater value for diluents provided by Bio-Rad (5.89 mS cm⁻¹) and Grifols (5.09 mS cm⁻¹), than by Ortho (3.03 mS cm⁻¹). Grey et al.¹⁶ reported that higher conductivity of ID-CellStab (Bio-Rad) could be the origin of false negative results.

5. Conclusions

In conclusion, the Grifols DG Gels system is safe for routine pre-transfusion compatibility procedures (antibody screening and identification) in blood transfusion.

Using more vials of reagent red blood cells by Grifols DG Gel when compared to other methods used in the laboratory increases the sensitivity for some antibody specificities, particularly anti-Jk^a. This could have major impact on the prevention of delayed transfusion reactions.

6. References

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VALIDACIJA TESTOVA PRIJETRANSFUZIJSKOG ISPITIVANJA PRETRAŽIVANJA I IDENTIFIKACIJE ANTIERITROCITNIH PROTUTIJELA PRIMJENOM DG GEL KARTICA

Sažetak

Uvod

Testovi za predtransfuzijsko ispitivanje razlikuju se prema osjetljivosti i specifičnosti i trebalo bi ih validirati prije primjene za rutinski rad. Cilj ove studije bio je procijeniti dijagnostičku točnost sustava aglutinacije u mikrostupcu Grifols DG Gel i usporediti podatke s još dva sustava aglutinacije u mikrostupcu koji se primjenjuju u našem laboratoriju: Ortho BioVue i Bio-Rad. Posebna pozornost posvećena je upotrebi više bočica test eritrocita kod sustava Grifols DG Gel u usporedbi s drugim sustavima kako bi se istražilo povećava li se osjetljivost za klinički značajna protutijela.

Materijal i metode

Svi uzorci testirani su paralelno karticama Grifols DG Gel, Ortho BioVue i Bio-Rad prema uputama proizvođača. Uzorci su obrađeni ručno. Ispitivanja su obavili obučeni i iskusni djelatnici. Ukupno je provedeno 419 ispitivanja na 302 uzorka.

Rezultati

Podudarni rezultati između sustava Grifols DG Gel i ostala dva sustava dobiveni su u 93,8 % ispitivanja. Za pretraživanje antieritrocitnih protutijela sustavom Grifols DG Gel osjetljivost je bila 97,53 %, specifičnost 100 %, prediktivna pozitivna vrijednost 100 % i prediktivna negativna vrijednost 97,73 %. Za identifikaciju specifičnosti protutijela točnost za sustav Grifols DG Gel bila je 96,03 %, 97,22 % za Ortho BioVue i 94,44 % za Bio-Rad.

Zaključci

Sustav Grifols DG gel pokazuje visoku dijagnostičku točnost i siguran je za predtransfuzijsko ispitivanje. Upotrebom više bočica test eritrocita sustavom Grifols DG Gel u usporedbi s drugim sustavima povećava se osjetljivost za neke specifičnosti protutijela, posebno anti-Jk^a. To bi moglo imati velik utjecaj na prevenciju odgođenih transfuzijskih reakcija.

Ključne riječi: evaluacija programa, krvne grupe i crossmatching, testovi hemaglutinacije, eritrociti, aloantitijela