Performance of Automated Chemiluminescence Assay for Antiphospholipid Antibody Testing

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Background: Detection of antiphospholipid antibodies (aPL) can be considered problematic due to assay variability and reagent sensitivity, high false-positive and false-negative rates, and lack of assay standardization. Therefore, utilizing an automated system can improve reproducibility and reduce interlaboratory variation. Here, we evaluated the analytical performance of the new automated ACL AcuStar chemiluminescence assay (Instrumentation Laboratory, USA). This was compared to the results of a panel analyzed with the QUANTA Lite ELISA (INOVA Diagnostics Inc., USA).

Methods: We evaluated the inter-assay precision, linearity, and carry-over between the two methods, ACL and ELISA. A reference range study for each of the anticardiolipin (aCL) and anti- β_2 glycoprotein-I ($\alpha\beta_2$ GPI) IgG and IgM antibodies were performed using 135 healthy patient samples, which served as controls. We then compared the accuracy among the AcuStar and ELISA systems via four aPL tests. For this comparison, 69 patient samples suspected of an autoimmune disorder were used as the experimental panel.

Results: The AcuStar analyzer showed excellent precision, linearity, and carry-over for all four assays. The calculated cutoff values were 20.3 U/mL for aCL IgG, 20.3 U/mL for aCL IgM, 26.3 U/mL for $\alpha\beta_2$ GPI IgG, and 11.9 U/mL for $\alpha\beta_2$ GPI IgM. The consensus between AcuStar and ELISA results were generally comparable. Total agreement varied between 82.6% and 95.7%, and kappa values showed moderate to good agreement.

Conclusions: Our study demonstrates that the new AcuStar chemiluminescence assay showed better performance. This automated system leads to improved reproducibility and reduces interlaboratory variability.

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Key Words: Antiphospholipid syndrome, Anticardiolipin antibodies, Anti- β_2 glycoprotein-I antibody, Automation, Chemiluminescence assay

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INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by arterial or venous thrombosis and/or pregnancy complications due to the persistent presence of antiphospholipid antibodies (aPL). These aPL are naturally occurring heterogeneous autoantibodies that bind to phospholipid-bound proteins [1-3]. aPL associated with APS includes lupus anticoagulant (LA), anticardiolipin (aCL), and anti- β_2 glycoprotein-I ($\alpha\beta_2$ GPI)

IgG or IgM antibodies.

To make a conclusive diagnosis of APS, at least one of the clinical and laboratory criteria need to be met [4,5]. Laboratory abnormality must be present on two or more occasions and at least 12 weeks apart. Systematic reviews have reported that LA is a stronger risk factor for both thrombosis and obstetric complications compared to aCL or $\alpha\beta_2$ GPI antibodies [1-5]. However, three aPL have now been associated with the highest risk for thrombosis and so can be implemented in laboratory criteria for APS [1-

5]. Thus, evaluation of patients using aPL profile rather than a separate test may be more useful in assessing thrombotic risk.

The laboratory identification of aPL can be problematic because the available tests have sensitivity and specificity variability, poor reproducibility, and a lack of standardization [6–9]. Currently, aCL and a β_2 GPI antibodies have been detected by an ELISA; however, recently developed automated platforms have been introduced [10–12]. The introduction of an automated system can improve reproducibility and reduce interlaboratory variation. In this study, we evaluated the analytical performance of a new automated chemiluminescence assay (HemosIL ACL AcuStar aPL assay; Instrumentation Laboratory, Bedford, MA, USA) and compared the results of a panel (aCL IgG, aCL IgM, a β_2 GPI IgG, and a β_2 GPI IgM) with the currently available ELISAs.

MATERIALS AND METHODS

1. Samples

We included samples from 69 patients, who were referred for the evaluation of autoimmune disorders such as systemic lupus erythematosus (SLE) or rheumatoid arthritis, hypercoagulability, and cardiovascular diseases. Venous blood samples were collected in serum separation tubes, VACUETTE (Greiner Bio-One GmbH, Kremsmunster, Austria) and the obtained serum samples after centrifugation were stored at -80°C for further analysis. Samples from the 135 healthy controls (65 women and 73 men; age, 43.8 ± 11.1 years) were also collected for the calculation of reference ranges. Informed consents were obtained from all patients prior to the study.

2. Antiphospholipid Antibody Assays

The HemosIL AcuStar aPL assay uses a two-step immunoassay method based on chemiluminescence technology. The assay panel includes aCL IgG, aCL IgM, a β_2 GPI IgG, and a β_2 GPI IgM. Magnetic particles are coated with cardiolipin complexed with human β_2 GPI in

aCL antibody test, and human β_2 GPI alone in a β_2 GPI antibody test. These antigen-coated magnetic particles capture the corresponding aPL IgG and/or IgM in the samples. An isoluminol-labeled secondary antibody in the tracer then binds to the captured antibodies, resulting in an emission of light proportionate to the concentration of the antibodies. The emitted light is measured in relative light units, and all aPL assays are standardized to a cutoff of 20 U/mL.

ELISA of aCL and a β_2 GPI antibodies was performed using the QUANTA Lite ACA and β_2 GPI kit (INOVA Diagnostics Inc., San Diego, CA, USA) according to the manufacturer's instructions. Polystyrene microwell plates are coated with purified cardiolipin antigen complexed with bovine β_2 GPI in aCL antibody assay, and purified β_2 GPI antigen alone in a β_2 GPI antibody test. Optical absorbance was measured on a Microplate Reader Model 680 (Bio-Rad Laboratories, Hercules, CA, USA). Test results were expressed semi-quantitatively in standard units, and the cutoff value for the positive results was assigned to >20 units for all aPL tests.

3. Evaluation of Analytical Performance Evaluation

Inter-assay precision was assessed using the low and high control materials according to the Clinical and Laboratory Standards Institute (EP05-A2) [13]. Each control was analyzed in duplicate for 5 days with two runs a day. Linearity study of dilution recovery was performed using clinical samples according to CLSI EP06-A [14]. Two serum samples with concentrations within $\pm 10\%$ of the upper limit of analytical measurement range (AMR) and within $\pm 50\%$ of the lower limit of AMR were proportionately mixed and tested in duplicates. We also evaluated percent carry-over using one normal and one high abnormal sample. A reference range study, for each of AcuStar aPL tests, was performed using 135 healthy control samples according to CLSI EP28-A3c [15]. The cutoff values of our laboratory were assigned at the 99th percentile. We compared the results for aCL and a β_2 GPI IgG and IgM obtained with AcuStar and ELISA in 69 samples in accordance with CLSI EP09-A2 [16]. The agreement percentages and Cohen's kappa values were

calculated.

4. Statistical Analysis

Statistical analysis was performed using the MedCalc Software ver. 9.3 (MedCalc Software bvba, Ostend, Belgium) and EP Evaluator Release 10 (Data Innovations LLC, South Burlington, VT, USA). We also used Microsoft Office Excel 2007 (Microsoft Co., Redmond, WA, USA). A P -value <0.05 was considered as significantly different.

RESULTS

1. Precision, Linearity, and Carry-Over

The AcuStar aPL assay panel was evaluated for several analytical performance characteristics including precision, linearity, and carry-over. Table 1 shows within run and total % CV at low and high concentration levels. AcuStar assays demonstrated within run and total CV of $<7.0\%$ and $<9.0\%$, respectively. The AcuStar analyzer showed excellent linearity for all four assays evaluated, within the

allowable systemic errors of 10.0% (1.7% to 4.5%). The AMR specified by the manufacturer was $2.6-2,024$ U/mL for aCL IgG, $1.0-774$ U/mL for aCL IgM, $6.4-6,100$ U/mL for $\text{a}\beta_2\text{GPI}$ IgG, and $1.1-841$ U/mL for $\text{a}\beta_2\text{GPI}$ IgM, while reportable ranges validated in this study were $2.6-40,480$ U/mL, $1.0-15,480$ U/mL, $6.4-122,000$ U/mL, and $1.1-16,820$ U/mL, respectively. The carry-over was also all within $\pm 1.0\%$ (-0.8% to 0.2%).

2. Reference Ranges

The upper reference limits were calculated within the 99th percentile of the 135 healthy control values. The cutoff value of the manufacturer is 20 U/mL, whereas calculated cutoff values of AcuStar assays were 20.3 U/mL for aCL IgG, 20.3 U/mL for aCL IgM, 26.3 U/mL for $\text{a}\beta_2\text{GPI}$ IgG, and 11.9 U/mL for $\text{a}\beta_2\text{GPI}$ IgM, respectively.

3. Method Comparison with ELISA

Patient samples in the AcuStar assay were analyzed with two different cutoffs, our laboratory's as well as the manufacturer's cutoffs. For the ELISA, the manufacturer's cutoffs were applied. With the our laboratory's cutoffs, 3 (4.3%) aCL IgG, 9 (13.0%) aCL IgM, 3 (4.3%) $\text{a}\beta_2\text{GPI}$ IgG, and 10 (14.5%) $\text{a}\beta_2\text{GPI}$ IgM results were positive in the AcuStar assay. The ELISA resulted in 6 (8.7%) aCL IgG, 13 (18.8%) aCL IgM, 9 (13.0%) $\text{a}\beta_2\text{GPI}$ IgG, and 11 (15.9%) $\text{a}\beta_2\text{GPI}$ IgM positive results. Thirty discordant results were observed between the two methods, 3 aCL IgG (only ELISA positive), 12 aCL IgM (8 ELISA alone and 4 AcuStar alone positive), 6 $\text{a}\beta_2\text{GPI}$ IgG (only ELISA positive), and 9 $\text{a}\beta_2\text{GPI}$ IgM (5 ELISA alone and

Table 1. Within run and total CV of the AcuStar assay

	aCL IgG	aCL IgM	$\text{a}\beta_2\text{GPI}$ IgG	$\text{a}\beta_2\text{GPI}$ IgM
Low control				
Within run % CV	6.2	2.9	6.4	5.3
Total % CV	8.6	3.0	7.7	5.6
High control				
Within run % CV	4.3	1.8	6.6	6.0
Total % CV	6.1	2.5	7.0	6.5

Abbreviations: aCL, anticardiolipin antibodies; $\text{a}\beta_2\text{GPI}$, anti- β_2 glycoprotein-I antibodies.

Table 2. Percentage agreement and kappa values (95% confidence interval) of the AcuStar assay

	aCL IgG	aCL IgM	$\text{a}\beta_2\text{GPI}$ IgG	$\text{a}\beta_2\text{GPI}$ IgM
In-house cutoffs				
Agreement (%)	95.7 (88.0–98.5)	82.6 (72.0–89.8)	91.3 (82.3–96.0)	87.0 (77.0–93.0)
Kappa value	0.65 (0.26–1.04)	0.36 (0.02–0.69)	0.47 (0.06–0.87)	0.50 (0.19–0.80)
Manufacturer's cutoffs				
Agreement (%)	95.7 (88.0–98.5)	82.6 (72.0–89.8)	88.4 (78.8–94.0)	91.3 (82.3–96.0)
Kappa value	0.65 (0.26–1.03)	0.36 (0.02–0.69)	0.37 (0.00–0.78)	0.62 (0.33–0.91)

Abbreviations: aCL, anticardiolipin antibodies; $\text{a}\beta_2\text{GPI}$, anti- β_2 glycoprotein-I antibodies.

Fig. 1. Comparison between the AcuStar assay and ELISA for (A, B) aCL and (C, D) aβ₂GPI (IgG and IgM). Abbreviations: aCL, anticardiolipin antibodies; aβ₂GPI, anti-β₂ glycoprotein-I antibodies; GPL, IgG anticardiolipin units; MPL, IgM anticardiolipin units; SGU, IgG aβ₂GPI units; SMU, IgM aβ₂GPI units.

4 AcuStar alone positive) tests, respectively. Table 2 shows the analytical agreement of the AcuStar aPL assay panel compared with the ELISA. Total agreement varied between 82.6% and 95.7%, and kappa values showed fair to good agreement.

Using the manufacturer's cutoffs, 3 (4.3%) aCL IgG, 9 (13.0%) aCL IgM, 5 (7.2%) aβ₂GPI IgG, and 7 (10.1%) aβ₂GPI IgM results were positive in the AcuStar assay. Discordant results in aCL IgG and IgM were the same in our laboratory's cutoffs, and differed only in aβ₂GPI IgG (6 ELISA alone and 2 AcuStar alone positive) and aβ₂GPI IgM (5 ELISA alone and 1 AcuStar alone positive). However, the analytical agreement and kappa statistics were comparable between the two different cutoffs.

We also compared the numerical test results between AcuStar and ELISA using a Pearson correlation coefficient. In Fig. 1, all assays showed significant correlation determined by correlation coefficient r values ($P < 0.0001$). Between AcuStar and ELISA, both aCL and aβ₂GPI showed better correlation for IgG than for IgM.

DISCUSSION

APS is a heterogeneous autoimmune disorder characterized by a wide range of clinical features, primarily thrombotic or obstetric complications. These clinical manifestations lack specificity. Therefore, a defining feature of APS is persistent aPL, being able to identify

these circulating antibodies is a necessity for correct diagnosis [5-9,17].

The laboratory detection of aPL can be problematic due to poor assay reproducibility and the lack of standardization. In relation to these issues, guidelines for laboratory identification of aPL have been published and updated by international working groups [4-6,8]. Recommendations covering the contributing factors include standards, calibration, and assay-specific. Application of these guidelines can help in implementing the best practices and the standardization of the assays.

Besides conventional ELISA, new platforms and detection technologies have been introduced [10-12,18-22]. The new automated platforms are expected to improve reproducibility and reduce interlaboratory variation.

AcuStar assays demonstrated within run and total CV of <7.0% and <9.0%, respectively. Precision is an important requirement, especially for automated analyzers; therefore, a between run imprecision of <10% is recommended [5,6,8,9,17]. The AcuStar analyzer showed excellent linearity for all four assays evaluated, within the allowed systemic error of 10.0% (1.7% to 4.5%). The carry-over was all within $\pm 1.0\%$ (-0.8% to 0.2%). The AcuStar allowed for a more broad reportable range for all four aPL assays compared to the ELISA studies. If testing automatically extended in automated re-dilution, 20 times of the cutoff could be obtained as compared to 6 to 10 times their respective cutoff values in currently available ELISAs [11].

According to the guidelines, it is recommended that laboratories determine their own in-house cutoff values by the 99th percentile of a healthy population of at least 120 healthy patient samples. In our study, calculated cutoffs were close to those of the manufacturer and only differed for $\text{a}\beta_2\text{GPI IgM}$ (11.9 U/mL versus 20 U/mL, respectively). Van Hoeske et al. [18] also reported similar cutoff values between in-house and manufacturer, while Chung et al. [21] found lower cutoffs for aCL IgG (13.5 U/mL) and $\text{a}\beta_2\text{GPI IgM}$ (12.6 U/mL). This discrepancy among the cutoff values could be due to the difference in demographics of the population samples evaluated by the laboratory and those of reference population evaluated

by the manufacturer. This inconstant variation is an indication that a reestablishment of reference range is necessary [6]. In addition, local cutoffs should be validated through a clinical approach whenever feasible [5].

The agreements between AcuStar and ELISA results were generally good. Total agreement varied between 82.6% and 95.7% and kappa values showed moderate to good agreement, regardless of the manufacturer's or in-house cutoffs. Our findings are in accordance with the results of other studies that investigated the chemiluminescence assays [11,12,18,21]. In contrast to our studies, Gutensohn et al. [19] utilized five different immunoassays to detect aCL and $\text{a}\beta_2\text{GPI IgG/IgM}$ in SLE patients. In their study, a poor to moderate accordance was reported. This discordance was explained as differences between the antibodies used by the manufacture as well as the differences in patient groups selected, resulting in a difference of cutoff values. In our study, the overall agreement between AcuStar and ELISA was better for aCL and $\text{a}\beta_2\text{GPI IgG}$ than for IgM. Also both aCL and $\text{a}\beta_2\text{GPI}$ showed better correlation for IgG than for IgM. From the literature, IgM antibodies are known to be less often associated with thrombosis than IgG, and clinical utility is higher for IgG isotype [5,6,9,17,23]. The current classification criteria require IgG as well as IgM isotype testing for both aCL and $\text{a}\beta_2\text{GPI}$, although there is an ongoing debate about the value of IgM aPL. It is also possible that IgM rheumatoid factor (RF) has contributed to false positivity for IgM isotype aCL and $\text{a}\beta_2\text{GPI}$ results. Thus, we need to address IgM RF interference when interpreting IgM aPL results.

In conclusion, these data suggest that the new AcuStar chemiluminescence assay shows good performance features. The automation can improve the reproducibility allowing for reduction in interlaboratory variation. We are now planning future studies to determine the clinical significance of aPL.

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항인지질항체 측정을 위한 자동화학발광 검사법의 수행능 평가

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동아대학교병원 진단검사의학과

배경: 항인지질항체의 측정은 검사법과 시약의 감수성의 차이, 높은 위양성 및 위음성률, 그리고 표준화의 부족 등과 같은 문제점이 있다. 자동화 장비를 사용하면 재현성을 높이고, 검사실 간 오차를 줄일 수 있을 것이다. 본 연구에서는 최근 국내 도입된 ACL AcuStar 화학발광검사장비의 수행능을 평가하고, 항인지질항체 결과를 QUANTA Lite ELISA 분석과 비교하였다.

방법: 정밀도, 직선성 및 잔재효과를 평가하였다. 135명의 대조군 검체를 사용하여 항카디오리핀 (anticardiolipin, aCL)과 항베타2당단백 (anti- β_2 glycoprotein-I, a β_2 GPI) IgG 및 IgM 항체의 참고치를 설정하였다. 또한 69명의 환자 검체에서 얻은 네 가지 항인지질항체 검사결과를 AcuStar와 ELISA 검사법 사이에 비교하였다.

결과: AcuStar 검사는 네 가지 검사에 대해 모두 매우 우수한 정밀도, 직선성 및 잔재효과를 나타내었다. 참고치는 각각 aCL IgG 20.3 U/mL, aCL IgM 20.3 U/mL, a β_2 GPI IgG 26.3 U/mL, 그리고 a β_2 GPI IgM은 11.9 U/mL이었다. AcuStar와 ELISA 사이의 일치율은 전반적으로 우수하였으며, 총 일치율은 82.6%에서 95.7%였고, 카파값은 중등도 내지 우수한 일치율을 보였다.

결론: 새로 도입된 AcuStar 화학발광검사는 우수한 수행평가 결과를 나타내었다. 자동화검사의 도입으로 재현성을 높이고, 검사실 간 오차도 줄일 수 있을 것이다.

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