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Analytical Evaluation of Platelet Aggregation Level on a Fully Automated Coagulation Analyzer CN-6000, and a Case Study of an Initial Absorbance of Platelet-rich Plasma

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Antiplatelet therapy has long been used as a practical treatment to prevent the development of thrombosis disease. The Dual antiplatelet therapy using adenosine diphosphate (ADP) receptor system inhibitors and acetylsalicylic acid (aspirin) has become standard therapy. With the development of stents in recent years, the management of antiplatelet therapy has become increasingly important. To assist in determining the effect of antiplatelet drug therapy, we have developed a scoring system using new parameters ADP-induced platelet aggregation level (APAL) and collagen-induced platelet aggregation level (CPAL) for the purpose of confirming the effect of ADP receptor inhibitors and aspirin respectively. Both APAL and CPAL are available on a fully automated coagulation analyzer CN-6000 (Sysmex Corporation, Kobe, Japan; hereinafter CN-6000, Sysmex). Measurement of platelet aggregation using a fully automated coagulation analyzer is expected to standardize procedures, reduce complexity, and create a more efficient testing option. In this study, we evaluated the within-run precision of APAL and CPAL on the CN-6000. The analyzer is equipped with a new function that automatically dilutes reagents in a stepwise manner providing the final dilution concentration. Additionally, we compared it with the existing instrument, the fully automated coagulation analyzer CS-5100 (Sysmex; hereinafter CS-5100) to provide a side-by-side analysis.

For the within-run precision evaluation, the APAL and CPAL coefficient of variation (CV) were determined using normal and abnormal samples with results of less than 3% and 8%, respectively. Also, excellent correlation results were observed against the CS-5100, r = 0.971 for APAL (n = 85) and r = 0.994 for CPAL (n = 82).

To provide sample information on platelet-rich plasma (PRP), the absorbance of PRP was evaluated using the preparation method recommended by the International Society of Thrombosis and Haemostasis. The normal reference range of PRP absorbance ("mOD") was calculated at a wavelength of 660 nm. The value ranged from 400.7–786.9 mOD at the starting point of PRP evaluation minus the mOD of platelet-poor plasma (PPP).

Notes: This article is based on current regulatory requirements in Japan. (as of February, 2024)
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Our study showed that the CN-6000 APAL and CPAL are reproducible and well correlated with the existing instrument, CS-5100. Since the CN-6000 is expected to reduce inter-procedural differences by automating reagent dilution steps, it will standardize future platelet aggregation testing.

INTRODUCTION

The measurement principle of *in vitro* platelet aggregation testing is light transmission aggregometry (LTA) which was developed by Born in 1962.[1] Since then, it has been used as the gold standard for the diagnosis of congenital platelet defects such as thrombasthenia and von Willebrand disease.[2] In recent years, it has been used in the management of antithrombotic therapy to assess antiplatelet drugs such as acetylsalicylic acid (aspirin), which is a COX-1 inhibitor, and clopidogrel and prasugrel, both of which are P2Y12 receptor inhibitors. The pharmacological effect of antiplatelet drugs is known to vary among individuals. For example, unresponsiveness to clopidogrel has been reported in approximately 20% of Asians because of CYP2C19 gene polymorphisms.[3-5] The term "aspirin resistance" is used for patients with a reduced antiplatelet effect with this drug. It has been reported that the following combination of conditions may cause aspirin resistance: Single Nucleotide Polymorphisms (SNP) affecting COX-1 and platelet function, inflammation and metabolic syndrome.[6-8] It has also been reported that the efficacy of aspirin was reduced in 27% of Japanese patients.[9] Therefore, it is thought to be clinically important to perform platelet aggregation testing to evaluate unresponsiveness to antiplatelet drugs and determine whether therapy should be discontinued/continued based upon test results.

LTA measurements require platelet-rich plasma (PRP) and platelet-poor plasma (PPP) samples. Both can be obtained by changing the centrifugation conditions. Moreover, it is a complicated and time-consuming test using semi-automated measurement devices. The test requires expert technicians to prepare and dispense reagents and samples. In recent years, fully automated coagulation analyzers, CS-5100, CS-2400, CS-2500, CS-2000*i*, and CS-2100*i* (Sysmex Corporation, Kobe, Japan; hereinafter Sysmex), were developed for routine tests such as Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), Fibrinogen (Fbg), Antithrombin (AT), and D-dimer. These fully automated coagulation analyzers can measure platelet aggregation.[10] Many evaluations have been performed comparing fully automated coagulation analyzers with existing semi-automated measurement devices. Findings show an acceptable correlation between the two types and the within-run precision is improved with the fully automated coagulation analyzers compared with semi-automated measurement devices.[11-15]

The interpretation of measurement results using LTA is also complicated and requires a high level of skill to perform. Particularly, when testing pharmacological effects of antiplatelet drugs, it is very difficult to judge changes in aggregation waveforms which are not as clear as those observed with congenital platelet defects. To solve this problem and provide easier interpretation of results, the two-concentration method was proposed.[16] This new method uses two concentrations of ADP and two concentrations of collagen to better capture changes in aggregation waveforms. In Japan, some devices utilize scoring indices for research use, which have been adopted by many institutions.[17] Therefore, we also developed a new scoring system, the platelet aggregation level (PAL), aimed to check the effect of antiplatelet drugs with Sysmex's fully automated coagulation analyzers.[18] The PAL is a function ancillary to the device that calculates an index as ADP-induced PAL (APAL). ADP was used to induce the aggregation of platelets and as collagen-induced PAL (CPAL) when collagen was used. Both APAL and CPAL are indices calculated using the area under the curve (AUC), This is the area of aggregation waveform with two concentrations that incorporate a unique index (***Fig. 1, 2***). APAL and CPAL calculations using
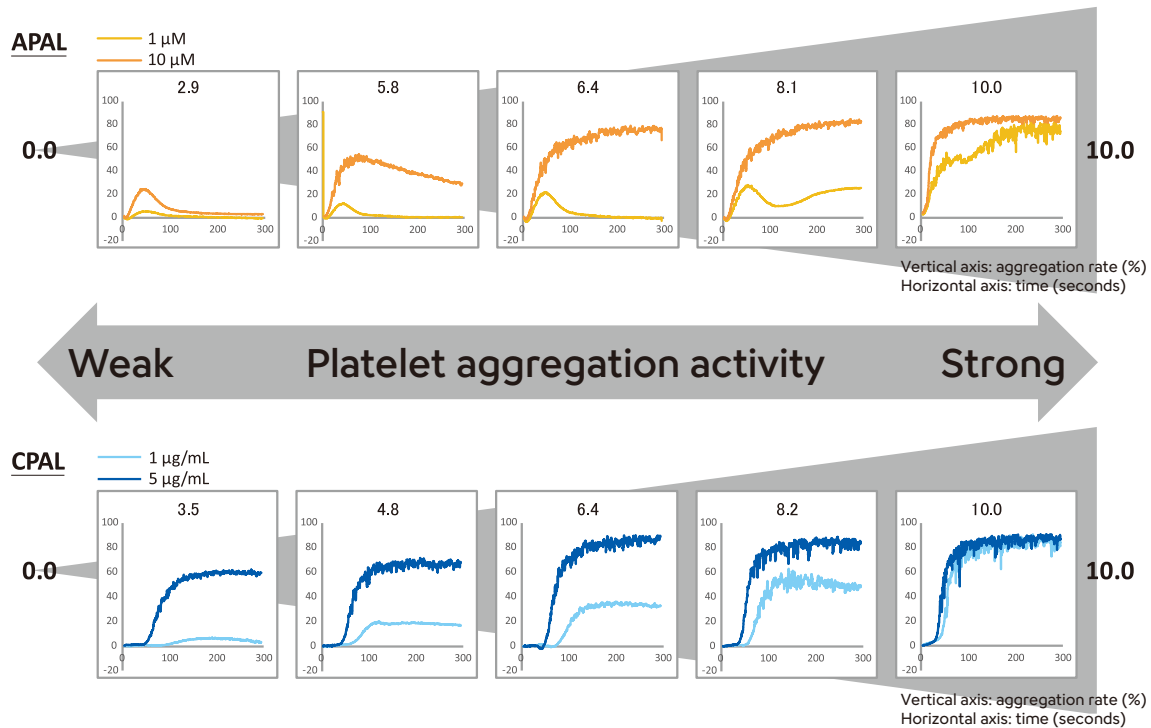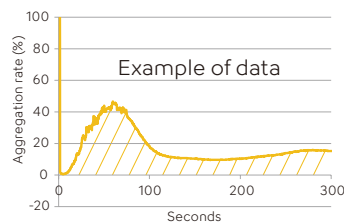
Fig. 1 *Examples of PAL scoring and aggregation waveforms*

APAL and CPAL are calculated from aggregation waveforms using two concentrations of ADP and collagen, respectively. The measurements change according to platelet aggregation activity.
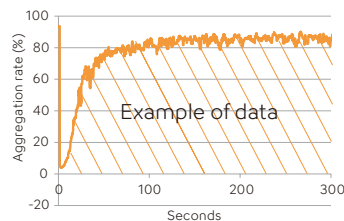
Fig. 2 *Outline of analysis methods for APAL and CPAL*

two-concentration methods already used in Japan, were compared and showed good results.[18–20]

Recently, a new fully automated coagulation analyzer CN-6000 (Sysmex; hereinafter CN-6000) was launched.[21, 22] The CN-6000 has a new function that measures platelet aggregation. It automates the serial reagent dilution process generating the correct final concentration. This dilution step is carried out manually for existing automated coagulation analyzers in the preparation of reagents before measurement. The added function improves the workflow and efficiency of the platelet aggregation test. The operator enters the reagent concentration, the number of runs, and then places the appropriate stock solution and diluents in the device. It then automatically prepares the serially diluted reagents (**Table 1**).[23]

A comparative analysis of platelet aggregation measurements using the CN-6000 and the CS-5100 has been reported. The findings showed good results[23] using reagent concentrations proposed by the International Society on Thrombosis and Hemostasis for screening congenital dysfunctions.[24] Moreover, as with existing fully automated coagulation analyzers, the CN-6000 has a function for calculating APAL and CPAL levels (**Fig. 3**).

In this study, we investigated the within-run precision of APAL and CPAL levels with the CN-6000 and how the results correlated with the CS-5100. We also investigated the absorbance (mOD) of PPP and PRP to provide sample information for platelet aggregation results.

Table 1 *Comparison of workflows of platelet aggregation tests*

Flow of measurement	Semi-automated	CS-5100	CN-6000
Collecting samples	Manual	Manual	Manual
Preparing PPP and PRP	Manual	Manual	Manual
Preparing reagents by serial dilution	Manual	Manual	Automated
Setting stirrers for cuvettes	Manual	Not needed	Not needed
Dispensing PPP and PRP to cuvettes	Manual	Automated	Automated
Adding inducers to cuvettes	Manual	Automated	Automated
Photometry	Automated	Automated	Automated
Outputting results	Automated	Automated	Automated

Changes from semi-automatic mode are shown in red.
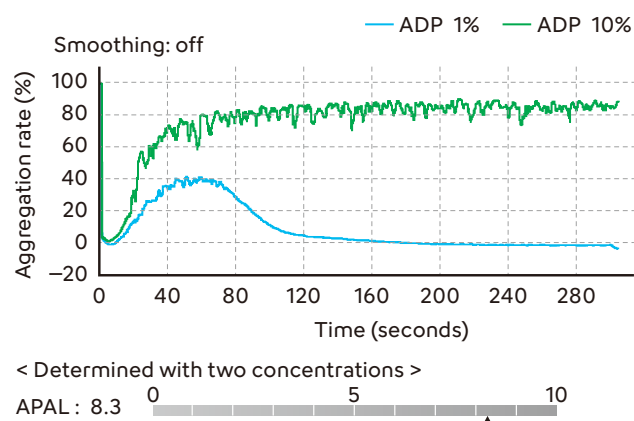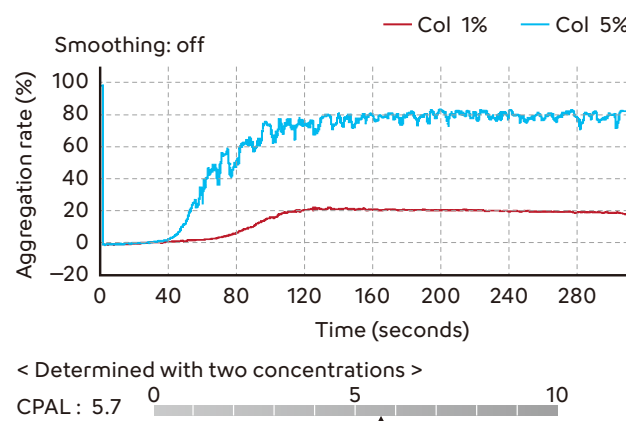

Fig. 3 *Examples of results of APAL/CPAL extracted from a device*

MATERIALS AND METHODS

1. Subjects

The present study was conducted after obtaining approval from the ethics committee of Sysmex Corporation (approval numbers: 2019-09 and 2015-78). Blood samples were collected from healthy in-house volunteers using Venoject II® Rtubes (Terumo Corporation), which is a blood collection tube containing 3.2% sodium citrate. To perform evaluations in accordance with the recommended guidelines reported by the International Society on Thrombosis and Haemostasis,[24] 10 mL of blood was taken from two tubes into a sterile round-bottom, centrifuge tube (Eiken Chemical Co., Ltd.) and centrifuged at $200 \times g$ for 10 minutes using the high-speed centrifuge Model 7000 (Kubota Corporation Co., Ltd.). After centrifugation, part of the supernatant was collected as PRP. The remaining blood was centrifuged at $1,500 \times g$ for 15 minutes, and the supernatant was collected as PPP.

PRP served as a normal sample and was void of any additives. Aspirin (Fujifilm Wako Pure Chemical Corporation) was added at final concentrations of 0.1–1.0 mM and/or cangrelor (AdooQ BioScience) was added at final concentrations of 0.01–0.2 µM which served as abnormal samples. For correlation tests, normal and abnormal samples were also prepared by the method described above to cover the measurement range.

2. Measurement devices and reagents

The CN-6000 was used to measure both within-run precision and correlation tests and the CS-5100 served as the predicate device.

Revohem ADP and Revohem Collagen (Sysmex) reagents were used for testing. The final reagent concentrations were adjusted automatically by the CN-6000 device to be 1 and 10 µM for ADP and 1 and 5 µg/mL for collagen. These are acceptable concentrations at which APAL and CPAL are automatically calculated, respectively.[18]

1) Within-run precision testing

Regarding the within-run precision testing, APAL and CPAL coefficients of variation (CV%) maximum aggregation rates (%) were obtained from five consecutive measurements using normal and abnormal samples.

2) Correlation testing

We performed measurements with ADP and collagen for 85 and 82 subjects, respectively. This set of measurements was performed once using the CN-6000 and once using the CS-5100 to obtain regression equations and correlation coefficients for maximum aggregation rates (%) and APAL/CPAL.

3) 95% confidence intervals of PPP and PRP

From the measurement results of 130 normal samples using the CN-6000, 95% confidence intervals were obtained for the mODs of PPP and PRP at the early phase of photometry and for difference between the mOD of PPP and that of PRP at the early phase of photometry using the analysis software Analyse-it (Analyse-it Software, Ltd.).

4) Comparative analysis of the mOD and platelet count of PRP

We measured the mOD and platelet counts of PRP from 70 normal samples. The mODs and platelet counts were each measured once to obtain both a regression equation and correlation coefficient. For mOD, data with the CS-5100 were used. The platelet count was calculated using the automated hematology analyzer XS series (Sysmex; hereinafter XS-1000*i*).

RESULTS

1) Within-run precision testing

The CV (%) of within-run precision was 2.1% for normal samples and 5.6% for abnormal samples in terms of the maximum aggregation rate with 1 µM of ADP; 1.8% for normal samples and 4.8% for abnormal samples in terms of the maximum aggregation rate with 10 µM; and 0.0% for

normal samples and 4.3% for abnormal samples in terms of APAL. Findings showed that 1.4% for normal samples and 7.3% for abnormal samples in terms of the maximum aggregation rate with 1 µg/mL of collagen: 1.9% for normal samples and 1.6% for abnormal samples in terms of the maximum aggregation rate with 5 µg/mL; and 0.0% for normal samples and 4.3% for abnormal samples in terms of CPAL (**Table 2**). These results were consistent with findings using the existing fully automated coagulation analyzers.[28]

2) Correlation testing

The correlation between a CN-6000 and CS-5100 was y = 1.00x + 3.85, r = 0.988 in terms of the maximum aggregation rate with 1 µM of ADP; y = 0.89x + 11.44, r = 0.955 in terms of the maximum aggregation rate with 10 µM of ADP; and y = 0.91x + 0.94, r = 0.971 in terms of APAL. It was y = 1.02x − 0.83, r = 0.996 in terms of the maximum aggregation rate with 1 µg/mL of collagen; y = 0.99x + 0.66, r = 0.972 in terms of the maximum aggregation rate with 5 µg/mL of collagen; and y = 1.00x − 0.08, r = 0.994 in terms of CPAL. These results showed good correlations (**Fig. 4**).

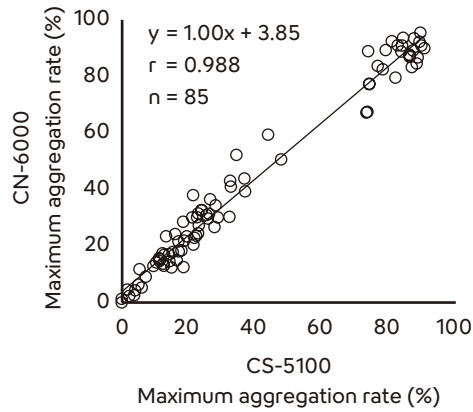***Table 2*** *Results of within-run precision*

A. ADP

	Normal samples			Samples spiked with cangrelor		
	1 µM Maximum aggregation rate (%)	10 µM Maximum aggregation rate (%)	APAL	1 µM Maximum aggregation rate (%)	10 µM Maximum aggregation rate (%)	APAL
run 1	92.2	90.8	10.0	20.2	63.6	5.3
run 2	90.9	93.6	10.0	19.1	70.0	5.7
run 3	93.6	91.1	10.0	17.9	66.4	5.2
run 4	89.0	91.0	10.0	19.6	72.0	5.3
run 5	89.6	94.2	10.0	17.8	68.2	5.1
Mean	91.1	92.1	10.0	18.9	68.0	5.3
SD	1.9	1.6	0.0	1.1	3.2	0.2
CV%	2.1	1.8	0.0	5.6	4.8	4.3

B. Collagen

	Normal samples			Samples spiked with aspirin		
	1 µg/mL Maximum aggregation rate (%)	5 µg/mL Maximum aggregation rate (%)	CPAL	1 µg/mL Maximum aggregation rate (%)	5 µg/mL Maximum aggregation rate (%)	CPAL
run 1	90.9	93.7	10.0	30.7	75.3	5.4
run 2	90.2	91.3	10.0	26.5	72.4	4.8
run 3	91.4	88.9	10.0	28.5	75.4	5.1
run 4	92.3	91.2	10.0	25.6	74.5	5.0
run 5	93.5	91.1	10.0	26.8	74.4	5.1
Mean	91.7	91.2	10.0	27.6	74.4	5.1
SD	1.3	1.7	0.0	2.0	1.2	0.2
CV%	1.4	1.9	0.0	7.3	1.6	4.3

A. ADP

a. 1 μM

y = 1.00x + 3.85
r = 0.988
n = 85

B. Collagen

a. 1 μg/mL

y = 1.02x − 0.83
r = 0.996
n = 82

b. 10 μM

y = 0.89x + 11.44
r = 0.955
n = 85

b. 5 μg/mL

y = 0.99x + 0.66
r = 0.972
n = 82

c. APAL

y = 0.91x + 0.94
r = 0.971
n = 85

c. CPAL

y = 1.00x − 0.08
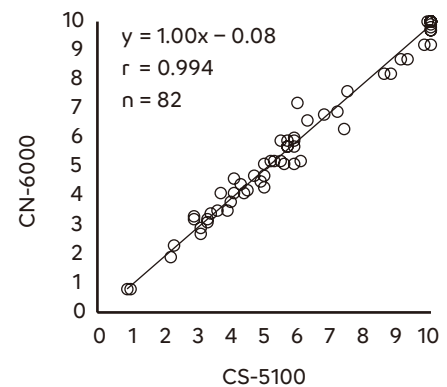r = 0.994
n = 82
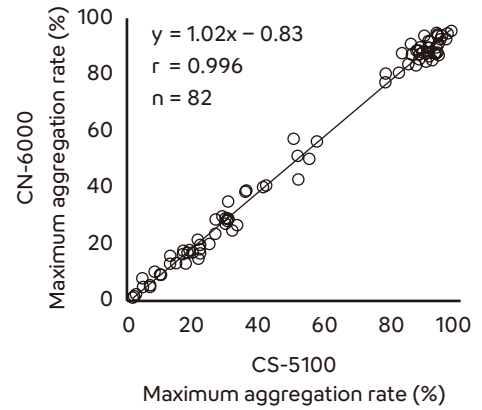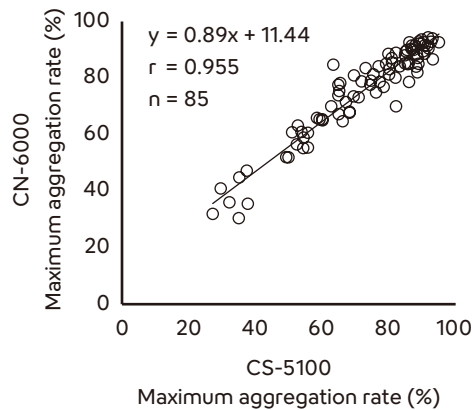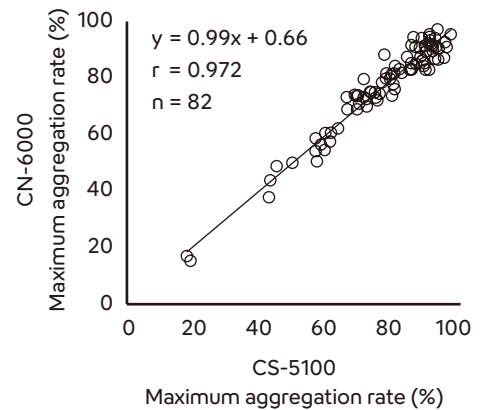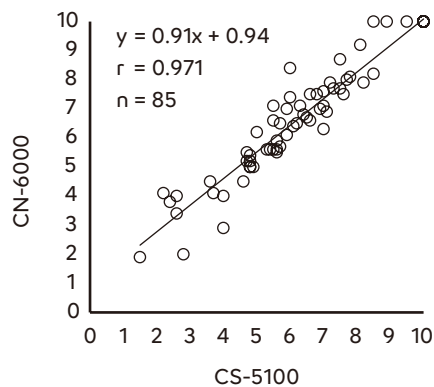
Fig. 4 *Correlation between CN-6000 and CS-5100*

3) Normal reference ranges for PPP and PRP

The 95% confidence intervals for the mOD of PPP and PRP at the early phase, and for values obtained by subtracting the mOD of PPP from the mOD of PRP at the early phase were −14.2–74.1, 419.0–828.4, and 400.7–786.9, respectively (***Fig. 5***). This allowed us to obtain confidence intervals in the normal reference range for samples prepared according to preparation conditions recommended by the International Society on Thrombosis and Haemostasis.

4) Comparative analysis of the mOD and platelet count of PRP

The correlation between the mOD and platelet count ($\times 10^4$/µL) of PRP was $y = 5.71x + 336.92$, $r = 0.570$, which confirmed the presence of a certain correlation (***Fig. 6***).
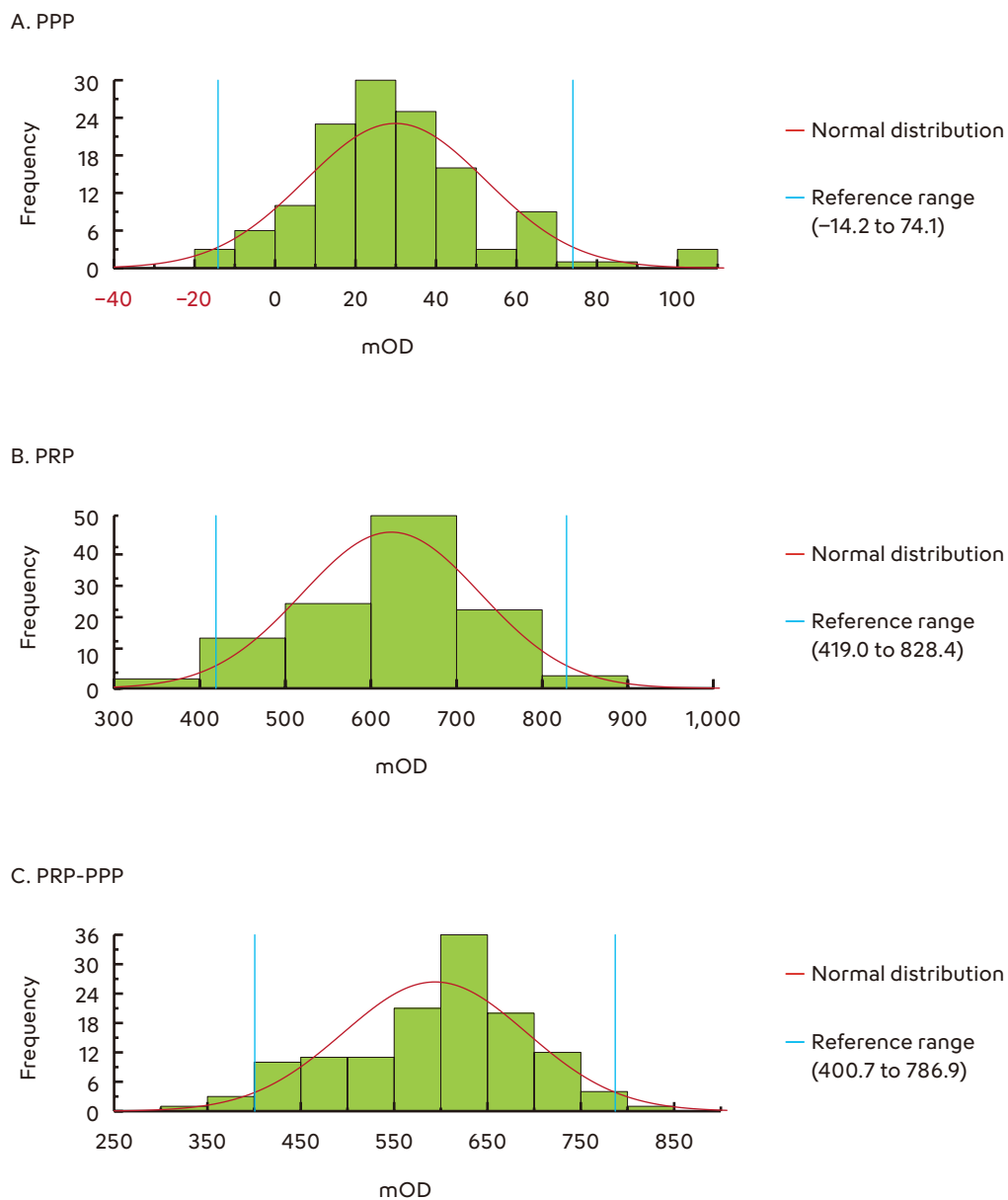

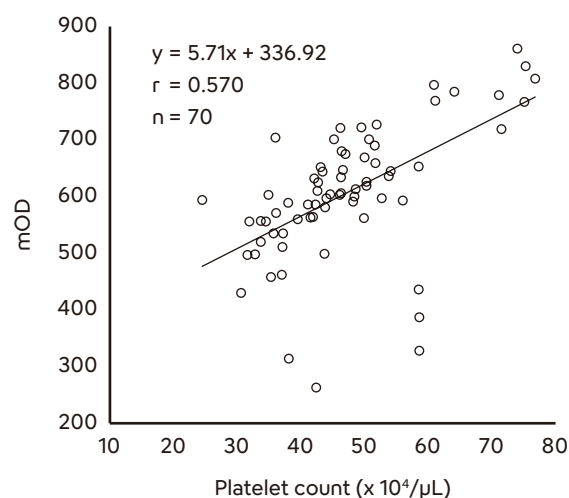***Fig. 5*** *Reference ranges of mOD of PPP and PRP*

Fig. 6 *Comparison of the mOD and platelet count of PRP*

DISCUSSION

It has been reported that changes with preoperative antiplatelet efficacy are related to perioperative ischemic/hemorrhagic complications.[25] It has been reported that East Asians are at a higher risk of bleeding compared with ethnic groups in other regions,[2] therefore it is very important to check the efficacy of antiplatelet drugs. Moreover, it has also been reported that decisions based on only one test leads to overestimation/underestimation[26] of drug dosing and that performing more than one platelet aggregation test is effective in reducing bleeding events.[27] Therefore, it is very important to measure platelet aggregation using an efficient and standardized method. These fully automated coagulation analyzers are routinely used for PT and APTT testing and are now able to measure platelet aggregation. Automated testing is cost-effective because a dedicated device is not needed which improves precision since no inter-operator differences exist. It is a reasonable method to standardize future testing.[11]

In this study, we evaluated the within-run precision of APAL and CPAL calculations, which were developed as useful indices to check the effects of antiplatelet drugs, using the CN-6000. Correlations between APAL and CPAL measurements were obtained using both the CN-6000 and the existing device, CS-5100. It has been reported that APAL calculations have an improved resolution, which enables the detection of patients with decreased antiplatelet activity. Detection cannot be determined by measurement using only one high concentration of ADP.[28] It has also been reported that for whole blood samples, a certain correlation was observed between measurement results with whole blood samples from a platelet aggregometer and the APAL index. The previously reported APAL concordance rate of APAL with the threshold of measurement results with whole blood samples using a platelet aggregometer for perioperative ischemic complications was previously reported as 90.9%. Additionally, the running cost is 1/25, indicating that similar evaluations can be done at lower a cost.[29]

In terms of within-run precision of APAL and CPAL, the CV (%) for normal samples was ≤3% and for abnormal samples was ≤8% (**Table 2**). CN-6000 measurements were similar to previously reported APAL results completed on the CS-5100[28] using concentrations for congenital platelet dysfunction proposed by the International Society on Thrombosis and Haemostasis.[10, 11, 23] In a clinical setting, antiplatelet drugs and anticoagulants are often used in combination, which was not performed in the present investigation. It has already been reported

that rivaroxaban and apixaban have no effect on aggregation with ADP or collagen.[30] Therefore, it is conceivable that these drugs also have no effect on APAL or CPAL measurements.

Correlation with results by the CS-5100 was very good. The results of the present investigation indicate that normal reference ranges can be used.[18, 28] Since racial differences among normal reference ranges have been surmised,[28, 31] it is desirable to obtain a normal reference range for each race.

With platelet aggregation tests, it is very important to keep different qualities of samples constant in order to obtain highly reliable results. The preparation of PRP and PPP is important in platelet aggregation testing. Since this step is a manual process we looked at standardizing this process. Therefore, in this study, we evaluated the mOD of PPP and PRP, the difference between the mOD of PPP and that of PRP when samples were prepared according to the recommended guidelines for handling/centrifugation conditions of specimens proposed by the International Society on Thrombosis and Haemostasis (**Fig. 5**) (for detailed information on centrifugation conditions, see *reference 32)*). The present investigation was conducted because we surmised the presence of a certain correlation between mOD and platelet counts, as shown in **Fig. 6**. For some specimens, the mOD dropped to a lower value compared with the regression line between mOD and platelet counts (**Fig. 6**). We attribute the decrease to specimen interference from turbid substances other than platelets (for example, chyle). As a result, the difference in mOD between PPP and PRP ranged from 400 to 787 (**Fig. 5**). The preparation of PRP intrinsically requires the management of centrifugal gravity on PRP. This means that when a blood collection tube with a different volume or a different centrifuge is used, the PRP gravity changes. The PRP position in the blood collection tube or the distance to the center of the centrifuge is altered. Therefore, it is necessary to choose an appropriate setting. We hope that the mOD example shown here will be helpful in determining centrifugation conditions, such as when a blood collection tube with a different volume is used or when a centrifuge has been changed.

CONCLUSION

As a method of checking the efficacy of antiplatelet drugs, APAL/CPAL indices ancillary to the CN-6000 analyzer showed good within-run precision. Additionally, APAL/CPAL measurements using the CN-6000 correlated well with APAL/CPAL levels using the existing device, CS-5100. By using the automated CN-6000 analyzer, standardization and improvement of platelet aggregation testing for antiplatelet therapy is expected. The CN-6000 reduces preparation variability by automating reagent dilution steps. The study provides 95% confidence intervals for the mOD of PPP and PRP to further standardize sample preparation according to the conditions recommended by the International Society on Thrombosis and Hemostasis. New scoring indices, APAL and CPAL, provide a simplified way to understand the efficacy of antiplatelet therapy and show they are reproducible and correlate well with the existing CS-5100 instrument.

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