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ORIGINAL ARTICLE

Evaluation of Collagen-Induced Platelet Aggregation Level Score Using an Automated Coagulation Analyzer

Keisuke Kitano [1], Tasuku Sakayori [1], Yukari Tsuboi [2], Hidekazu Ishida [2], Nobuo Arai [1], Kodai Uematsu [3, 4], Yutaka Komiyama [5], Yukiko Enomoto [3]

[1] *Sysmex Corporation, Kobe, Hyogo, Japan*
[2] *Division of Clinical Laboratory, Gifu University Hospital, Gifu, Japan*
[3] *Department of Neurosurgery, Gifu University Graduate School of Medicine, Gifu, Japan*
[4] *Department of Neurosurgery, Gifu Prefectural General Medical Center, Gifu, Japan*
[5] *Faculty of Health and Medical Sciences, Hokuriku University, Kanazawa, Ishikawa, Japan*

SUMMARY

Background: **Light-transmission aggregometry is the gold standard for assessing platelet function. The scoring system, designed based on the results obtained using two different concentrations of agonists on semi-automated analyzers, is commonly used to confirm the effects of antiplatelet drugs in Japan. Given the time-intensive and laborious nature of LTA, along with the lack of standardization across laboratories and devices, automated and consistent methods to monitor platelet function are imperative. Recently, we developed a new parameter and equipped an automated coagulation analyzer with it. In this study, a new parameter, "collagen-induced platelet aggregation level (CPAL)," was developed, and its basic performance was evaluated and compared with the maximum aggregation rate of 1.0 mM arachidonic acid (AA-MA) and the result of the VerifyNow aspirin assay, expressed in aspirin reaction units (ARU), performed on patients on antiplatelet therapy.**

Methods: **An automated coagulation analyzer was equipped with CPAL. CPAL is calculated as a score from 0.0 to 10.0 based on platelet aggregation patterns with 1.0 and 5.0 µg/mL collagen. Within-run precision was calculated by conducting five replicate analyses of the platelet-rich plasma (PRP) from healthy volunteers and 1.0 mM aspirin-spiked PRP. The dose-response effect of aspirin was evaluated using several concentrations of aspirin and PRP obtained from healthy volunteers. A comparative study was conducted using 62 PRP samples obtained from patients receiving antiplatelet therapy.**

Results: **The coefficient of variation in within-run precision was within 5% for CPAL. Aspirin treatment affected CPAL expression in a concentration-dependent manner. A significant correlation was observed between CPAL and AA-MA ($r = 0.70$, $p < 0.001$). However, a very weak or no correlation was observed between CPAL and ARU ($r = 0.17$, $p = 0.179$).**

Conclusions: **CPAL exhibits acceptable performance. It showed good correlation with AA-MA but not with the ARU of VerifyNow, which changed with slight differences in aspirin concentration. CPAL is a new platelet aggregation scoring system that may be used to monitor the effects of aspirin using an automated coagulation analyzer.**
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Correspondence:
Tasuku Sakayori, PhD, Senior Engineer
Application Support
Global Management
Sysmex Corporation
1-3-2 Murotani, Nishi-ku
Kobe 651-2241
Japan

Phone: + 81 789925860
Fax: + 81 769923274
Email: Sakayori.Tasuku@sysmex.co.jp

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KEYWORDS

platelet aggregation, light transmission aggregometry (LTA), automated coagulation analyzer, CPAL, aspirin

INTRODUCTION

Light-transmission aggregometry (LTA), a standard platelet aggregation test developed by Born in 1962 [1], relies on changes in light transmission during the stirred preparation of platelet-rich plasma (PRP). LTA is considered the gold standard method by the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis to assess platelet function for the diagnosis of congenital platelet dysfunction, such as thrombasthenia or von Willebrand disease [2]. This method has also been used for the management of antithrombotic therapy in recent years to monitor the effectiveness of antiplatelet agents, such as COX-1 inhibitors (e.g. acetylsalicylic acid [aspirin]) and P2Y12 receptor inhibitors (e.g. clopidogrel and prasugrel) [3–7]. LTA is a time- and labor-intensive technique restricted to specialized clinical laboratories. Furthermore, international surveys have regularly highlighted the lack of standardization in laboratory practices, which hinders the extrapolation of results to other centers because of the use of different concentrations of agonists [6,8]. A certain degree of variation is observed because of the differences between the reagents and devices used for LTA [9-12]. Therefore, to obtain reliable evidence, the reagents and devices must not be changed. Studies have shown that even when the reagent and its concentrations were identical, the results obtained differed with the instruments used [12]. To automate and produce stable results and thereby decrease the wastage of laboratory resources and time, we devised an automatic scoring system for ADP-induced platelet aggregation (APAL). Monitoring antiplatelet therapy is important for the diagnosis of patients who are hypo- or hyper-responders in terms of the risk of developing thrombosis or hemorrhage [13]. Patients who are hypo-responders to aspirin are considered to show “aspirin resistance,” which may be caused by the presence of single nucleotide polymorphisms that affect the functions of COX-1 and platelets, inflammation, and metabolic syndrome [14–16]. Therefore, platelet aggregation testing may be clinically important for assessing platelet reactions with antiplatelet agents or for deciding whether management of drug dosage is required.

Most studies using LTA for routine laboratory testing use arachidonic acid (AA) or collagen maximal aggregation (MA) to assess platelet response to aspirin [3, 17]. Recently, the VerifyNow aspirin assay, a point-of-care test that uses anticoagulated whole blood, has been used for predicting perioperative thromboembolic and hemorrhagic complications in patients treated with aspirin [18-20]. Various methods have been developed to assess the effectiveness of aspirin, leading to diverse results, which has rendered the establishment of a standard method difficult [18].

For patients undergoing cardiovascular and neurological surgeries, a scoring system that can aid clinicians in understanding the results is urgently required, so that the results can be utilized for perioperative applications. A method for classifying platelet aggregation patterns using two concentrations of agonists has been developed [21] and is popularly used in Japan [22,23]. Defining the relationship between two concentrations of a reagent requires a certain level of proficiency; thanks to a device that automatically unifies them to a single score, clinicians can now easily understand complex data. However, this is not a widely used global scoring system.

Similar to the concept of the APAL score, the collagen-induced platelet aggregation level (CPAL) score, ranging from 0.0 to 10.0 based on platelet activity from the aggregation pattern with 1 and 5 μg/mL collagen, has been recently developed and used to equip the Sysmex CN/CS series (Figure 1) [22].

The purpose of this study was to evaluate the newly developed CPAL method for precision and dose response to aspirin *in vitro* and compare the observations with the results of the AA and VerifyNow aspirin assays.

MATERIALS AND METHODS

Evaluation using samples from healthy individuals and aspirin-spiked samples (within-run precision and effect of aspirin spike)

This study was approved by the Sysmex Corporation Ethics Committee (approval no. 2015-62). Samples were obtained from healthy subjects who were not receiving any medication or were self-medicating with nonsteroidal anti-inflammatory drugs (i.e. aspirin or ibuprofen), after they had provided signed informed consent. Blood samples were prepared as previously described [22]. Briefly, Venoject II® tubes (Terumo Corp, Tokyo, Japan) were used for blood sampling, and the platelet count in PRP was determined using XS-1000i (Sysmex Corp, Kobe, Japan). Acetylsalicylic acid (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was added *in vitro* to healthy PRP (< 2% out of the total volume), and the mixtures were incubated at ambient temperature for 10 minutes prior to analysis. Acetylsalicylic acid was diluted with 100% ethanol (Wako Pure Chemical) to prepare aspirin, which had no effect on platelet aggregation at concentrations of up to 0.01%. The final concentrations of the antiplatelet agents are described in the figure legends.

LTA was performed using an automated blood coagulation analyzer (CS-5100). Original PRP samples without inducers were used for baseline readings, and 100% aggregation was defined as the absorbance of PRP with saline. Platelet aggregation was assessed using Revohem collagen (final concentration: 1 and 5 μg/mL) (Sysmex) and Revohem AA (final concentration: 1 mM) (Sysmex). CPAL score was automatically calculated and displayed by the software on the analyzers using the results of the 1 and 5 μg/mL collagen aggregation curve.

Within-run precision of 1 and 5 μg/mL collagen-MA and CPAL were determined by measuring each sample

five consecutive times in a single run. The healthy original PRP and that prepared with 1,000 μM aspirin were used.

The effect of aspirin was evaluated from the changes in CPAL and 1 mM AA-MA scores obtained from the measurement of PRPs, which were prepared in the presence of different concentrations of aspirin (250, 500, and 2,000 μM).

The Wilcoxon rank-sum test was performed using the JMP software (SAS Institute Inc., Cary, NC, USA). $p < 0.005$ was considered statistically significant.

Evaluation of the relationship between CPAL using clinical specimens and AA-MA and VerifyNow

All patients who underwent periprocedural antiplatelet therapy between December 2017 and June 2019 as elective neuroendovascular treatment, including carotid stenting, coil embolization, or the use of flow diverters for intracranial aneurysms, were included in this study. All participants signed informed consent forms after receiving explanations regarding the study's purpose. This study was approved by the Ethics Committee of the Gifu University School of Medicine (approval no. 29-217).

Blood samples were prepared as previously described [23]. Briefly, Insepack II-W collection tubes (SEKISUI MEDICAL Corp., Tokyo, Japan) were used for blood sampling, and PRP platelet counts were determined using XE-5000 (Sysmex Corp., Kobe, Japan). LTA was performed using an automated blood coagulation analyzer CS-2400 (Sysmex).

These samples were tested with 1 and 5 μg/mL collagen for CPAL and 1 mM AA-MA. Furthermore, they were tested using VerifyNow aspirin (Accumetrics, San Diego, CA, USA) POC system cartridges for aspirin reaction unit (ARU) values.

RESULTS

Within-run precision

Evaluation of within-run precision revealed that the values of the percentage coefficient of variation (CV%) for 1 and 5 μg/mL collagen-MA and CPAL were 3.1%, 2.7%, and 0.0% in PRP from healthy donors and 2.3%, 4.4%, and 4.3% in 1,000 μM aspirin-spiked PRP, respectively (Table 1). The aggregation curve confirmed the reproducibility of this method (Figure 2).

Effect of aspirin spike

We observed that both CPAL and AA-MA scores differed significantly between non-spike samples and those spiked with 250 μM, 500 μM, and 2,000 μM aspirin each. The CPAL score not only differed significantly between the 250 μM spiked and non-spiked samples ($p < 0.005$), but a decreasing trend was observed with increase in aspirin spikes. In contrast, the AA-MA score of the 250 μM aspirin-spiked sample was significantly lower than that of the non-spiked sample ($p < 0.005$), and it did not change even when the samples were spiked with up to 2,000 μM aspirin (Figure 3).

Relationship between CPAL score of clinical specimens and AA-MA and VerifyNow

A total of 60 patients (30 with carotid stenting and 30 with intracranial aneurysms) were screened for the study. The mean age of the patients was 72 years (36 males and 24 females). The clinical and biological characteristics of the patients at baseline are summarized in Table 2. Platelet reactivity in all patients was tested using VerifyNow and CS-2400. A significant correlation was observed between CPAL and AA-MA scores ($r = 0.70$; $p < 0.001$). In contrast, CPAL and ARU scores did not show any significant correlation, if not negligible ($r = 0.17$; $p = 0.179$) (Figure 4).

DISCUSSION

Preoperative antiplatelet therapy is associated with perioperative ischemic and bleeding complications. Moreover, the risk of bleeding is higher in East Asians than in other racial populations [24]. These facts indicate that confirming the effects of antiplatelet agents is critical. In addition, platelet aggregation can be over- or underestimated if judged using a single test [25], while multiple platelet aggregation tests can contribute to a reduction in bleeding events [26]. This suggests that platelet aggregation should be measured efficiently and in a standardized manner. A variety of measurement principles for confirming the effects of aspirin exist, which depend on the device used [18,27]. In some cases, AA or collagen may be used as LTA agonists [6,17]. Thus, a standard method has not yet been established, and many issues remain to be addressed.

We observed excellent within-run precision, with CV lower than 5%. In addition, others have found that the LTA system in an automated coagulation analyzer exhibits better reproducibility than the semi-dedicated device in routine clinical testing [11,12]. LTA is sample-specific; in other words, PRP cannot be frozen, and hence, cannot be transported to an outsourced laboratory for testing; therefore, it can only be performed in hospitals. Thus, automated LTA with the CPAL quantification system is suitable for monitoring the antiplatelet agents in a routine hospital setting more accurately.

We used an *in vitro* aspirin spike study to compare CPAL with AA-MA, which is widely used to confirm the effect of aspirin in LTA [6]. Treatment with aspirin affected the CPAL score in a concentration-dependent manner while simultaneously affecting the AA-MA score. These results suggested that AA is superior to other antiplatelet agents in distinguishing the presence of aspirin. Furthermore, CPAL may be used to quantify the results based on the effect of the aspirin spike. According to the results of this comparative study, the correlation between the AA-MA and CPAL scores was moderate. While the AA-MA score was 20% in most

Table 1. Within-run precision scores.

	Healthy sample			Aspirin-spiked sample		
	Collagen 1 µg/mL MA (%)	Collagen 5 µg/mL MA (%)	CPAL	Collagen 1 µg/mL MA (%)	Collagen 5 µg/mL MA (%)	CPAL
Run 1	92.0	90.7	10.0	23.5	74.8	5.0
Run 2	84.2	91.1	10.0	24.5	66.3	4.5
Run 3	90.4	86.5	10.0	24.1	67.6	4.5
Run 4	88.1	93.8	10.0	23.8	72.4	4.9
Run 5	86.6	92.0	10.0	22.9	71.3	4.7
Mean	88.3	90.8	10.0	23.8	70.5	4.7
SD	2.8	2.4	0.0	0.5	3.1	0.2
CV (%)	3.1	2.7	0.0	2.3	4.4	4.3

Table 2. Clinical characteristics of participants (n = 60).

Clinical characteristics	
Age	72 (35 - 88)
Men	36 (63.3%)
PLT count in PRP (10^4/µL)	28.5 (14.6 - 49.9)
WBC (µL)	6,261 (3,120 - 11,810)
RBC (10^6/µL)	4.1 (2.8 - 5.4)
Hemoglobin (g/L)	124 (81 - 168)
Hematocrit (%)	36.7 (24.2 - 48.0)
Medical history	
CAD	11 (18.3%)
PAD	4 (6.7%)
Stroke	23 (38.3%)
Antiplatelet drug	
SAPT	
Aspirin	6 (10.0%)
Clopidogrel	4 (6.7%)
Cilostazol	1 (1.7%)
DAPT	
Aspirin and Clopidogrel	34 (56.7%)
Aspirin and Cilostazol	5 (8.3%)
Clopidogrel and Cilostazol	3 (5.0%)
TAPT	
Aspirin, Clopidogrel, and Cilostazol	7 (11.7%)

Data are expressed as median (range) or n (%).
WBC white blood cell, RBC red blood cell, CAD coronary artery disease, PAD peripheral arterial disease, SAPT single antiplatelet therapy, DAPT dual antiplatelet therapy, TAPT triple antiplatelet therapy.

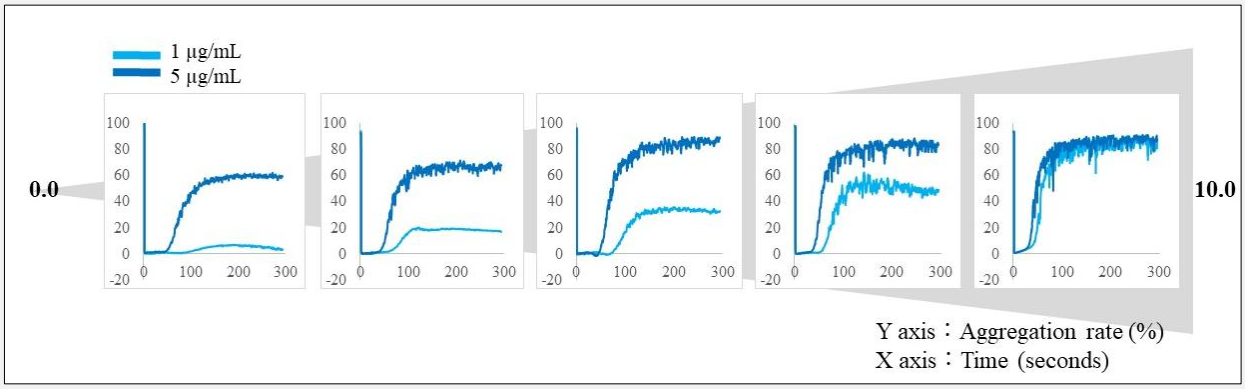

Figure 1. Examples of CPAL score calculated from the results of waveform results.

CPAL scores were calculated from the waveform results obtained using two concentrations of the agonist (1 and 5 µg/mL collagen). These scores increased with platelet aggregation activity.

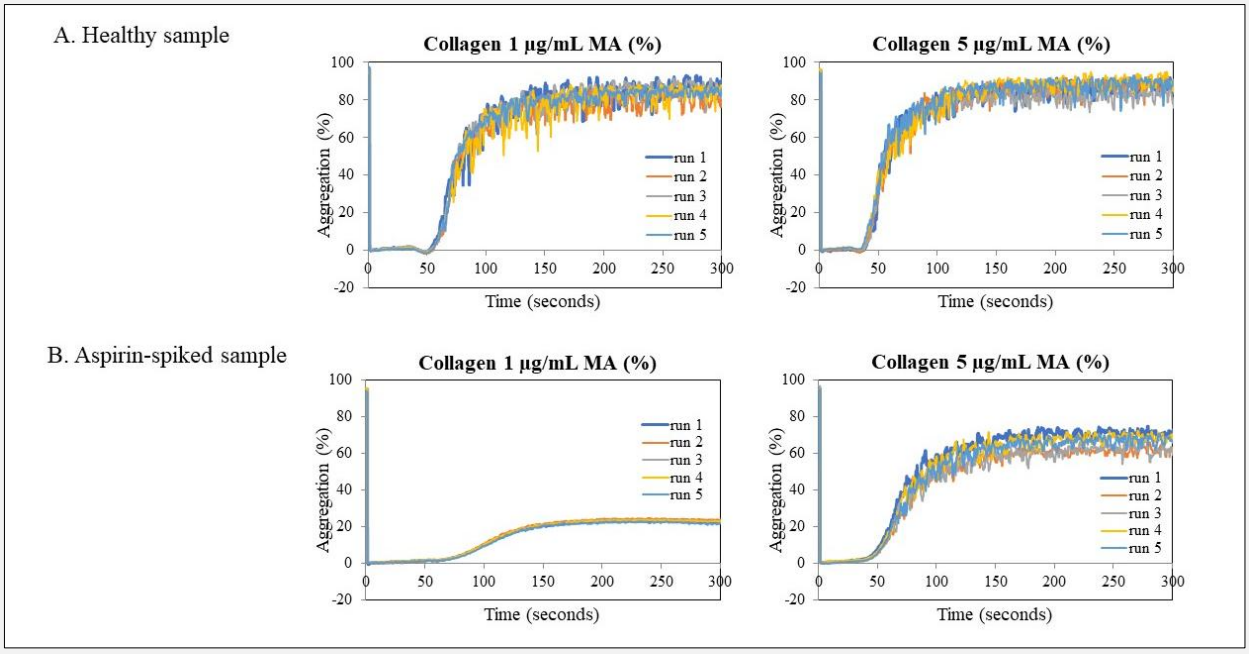

Figure 2. Within-run precision waveforms.

These waveform graphs superimpose the results of five consecutive measurements of the same sample at each collagen concentration. A Healthy and B aspirin-spiked samples were analyzed.

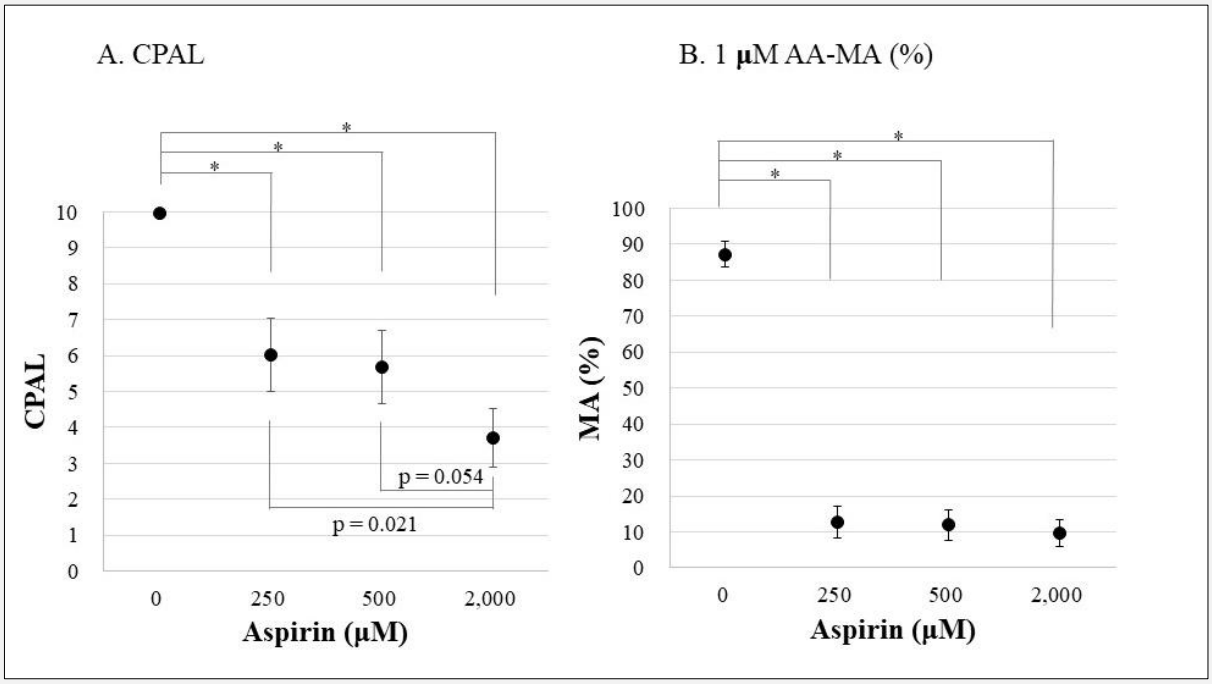

Figure 3. Effect of aspirin spike (*in vitro*).

A CPAL gently decreased depending on aspirin concentration, while B AA-MA decreased sharply. Each error bar shows 2 * standard error (SE) calculated from seven results of different donors. The asterisk means p < 0.005.

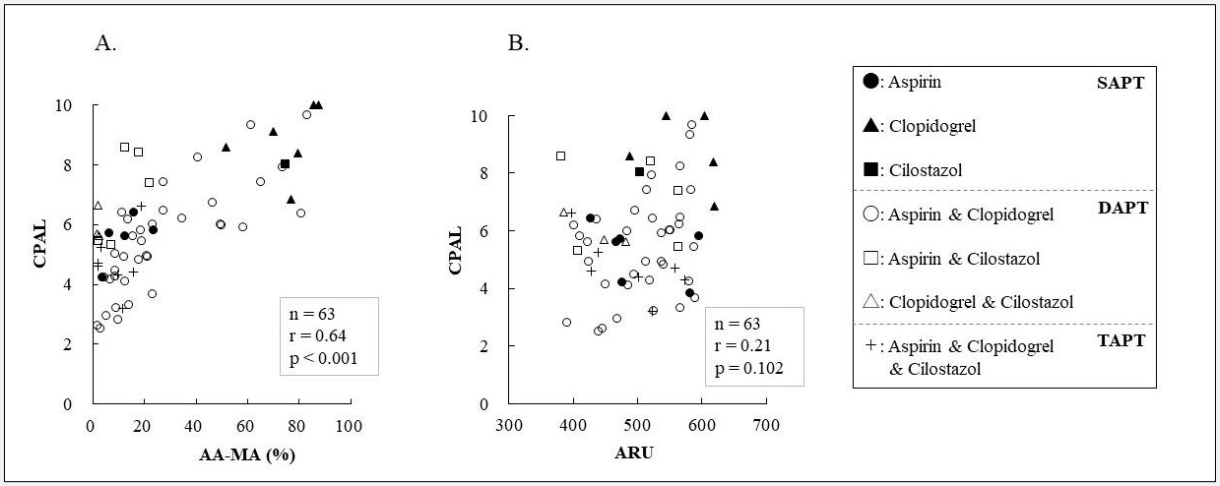

Figure 4. Correlation between CPAL, AA-MA, and VerifyNow (ARU).

A Graph comparing CPAL and AA-MA scores. B Graph comparing CPAL and ARU. n shows the number of samples and r shows the Pearson correlation coefficient of each graph.

samples, the CPAL rate varied widely, from 2 to 6, and the score was even under 20%. These results suggested that the CPAL calculation may be based on the effect of aspirin dosing, similar to the results of the aspirin spike evaluation.

The correlation between ARU and CPAL was r = 0.17, which was not significant. Previous studies have shown that the MA-AA of the LTA and ARU are not correlated [18,19], which was corroborated by our observations. Although ARU uses AA as an inducing agent, good correlation with LTA was not observed, presumably because of the differences among the samples or measurement principles. As mentioned in the other study, differences in reactivity between collagen-induced aggregation of LTA and ARU may be influenced by other factors such as fibrinogen and von Willebrand factor [28]. Aspirin is a COX-1 inhibitor. To understand the effect of aspirin, the effect of the administered P2Y12 inhibitors on the measurement results must be considered. However, we did not evaluate their effects on CPAL. A study has shown that clopidogrel, a P2Y12 inhibitor, is less affected by collagen than AA. Therefore, CPAL may be less affected by P2Y12 inhibitors than by AA. The CS/CN series offers the advantage of being a walk-away technology and requires smaller sample volumes than existing LTA instruments [29]. Unlike the conventional use of several concentrations of agonists, which complicates the interpretation of the results, CPAL requires only a fixed concentration of collagen and is suitable for LTA standardization. As these analyzers are used worldwide, we expect standardization of LTA in multicenter collaborative research in the future.

Our study has limitations. We did not test clinical samples before and after aspirin treatment. Only the CS-5100 and CS-2400 analyzers were included in the study; however, these findings are applicable to CS-2500, CN-3000, CN-3500, CN-6000, and CN-6500, which use the same analysis system and analytical software.

CONCLUSION

The newly developed CPAL system exhibited acceptable performance. The CPAL score showed good correlation with the AA-MA score, and it changed according to slight differences in aspirin concentration. CPAL is a new platelet aggregation scoring system that has the potential to monitor the effects of aspirin using an automated coagulation analyzer.

Source of Support:
This study was supported by Sysmex Corporation.

Declaration of Interest:
K. Kitano, T. Sakayori, and N. Arai are employees of Sysmex Corporation. Y. Komiyama is an external adviser of Sysmex Corporation.

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