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Original Research Article

Effect of clopidogrel on post-extraction clotting in patients on dual antiplatelet therapy

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Abstract

Purpose: *To evaluate the association between the platelet inhibition rate of clopidogrel (CLO-PIR) and post-extraction clotting status in DAPT patients.*
Methods: *Ninety (90) eligible patients scheduled for a single tooth extraction were enrolled in this study. The CLO-PIR and platelet inhibition rate of aspirin (ASA-PIR) were determined by thromboelastography platelet mapping assay. Post-extraction clotting assessments were performed, and a complete intra-alveolar clot formation within 30 min post-operation was defined as normal clotting. For clot formation exceeding 30 min, it was defined as prolonged bleeding.*
Results: *At a similar level of ASA-PIR, a higher proportion of patients with normal CLO-PIR (≤ 75 %) exhibited normal clotting, compared with those featuring high CLO-PIR (>75 %, p < 0.001). However, in patients with similar CLO-PIRs, the clotting results varied insignificantly, with increase in ASA-PIR. The effect of CLO-PIR was further validated using logistic regression analysis (odds ratio = 1.071, 95 % confidence interval: 1.024 - 1.120, p = 0.003), and receiver operating characteristic curve analysis revealed that a 78.6 % CLO-PIR was the rational cut-off point.*
Conclusion: *This study preliminarily demonstrates the prominence of high clopidogrel responsiveness in slowing the post-extraction clotting process in DAPT patients.*

Keywords: *Dual antiplatelet therapy, Clopidogrel responsiveness, Dental extraction, Post-extraction clotting, Thromboelastography platelet mapping assay, Platelet inhibition*

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INTRODUCTION

Nowadays, an increasing number of patients given dual antiplatelet therapy (DAPT) which is a combination of aspirin (ASA) and clopidogrel (CLO), have undergone dental extractions [1]. Compared with single antiplatelet treatment (SAPT) using ASA, the addition of CLO may prolong the postoperative clotting process [2]. Although some studies have indicated the controllability of increased bleeding in patients with DAPT maintenance [3], and some clinical guidelines have advised against the use of DAPT suspension to avoid thrombotic events [4], the supporting evidence is limited when compared with patients receiving ASA alone. Currently,

some oral surgeons still require patients to interrupt DAPT preoperatively owing to the insufficiency of relevant knowledge [5].

In SAPT patients with ASA continuation, the proportion of those who exhibit prolonged post-extraction bleeding (clotting time >30 min) generally ranges from 1.1 - 2.4 % [2,6]. However, whether or not patients continue DAPT preoperatively remains controversial. Related studies indicate that 4.2 - 9 % of those with sustained DAPT may present with obvious increase in bleeding [2,7], but a much higher proportion of 25 - 66.7% has also been reported [1, 6]. Given that the limited effect of ASA has been extensively reported [2,6], the inconsistent results after CLO addition may be attributable to individual variability in CLO responsiveness, which has not been fully considered in previous studies. Hence, it is essential to investigate the correlation between platelet inhibitory response to CLO and post-extraction clotting status.

Thromboelastography (TEG) is a monitoring system that records the dynamic processes of coagulation, while TEG platelet mapping (TEG-PM) is highly efficient in the detection of platelet function under antiplatelet therapies [8]. In TEG-PM, CLO and ASA responsiveness are indicated by the platelet inhibition rate (PIR), induced by adenosine diphosphate (ADP) and arachidonic acid (AA), respectively [9]. Currently, CLO- and ASA-PIR in TEG-PM have proven to be very reliable for the therapeutic assessment of antiplatelet therapies, and the vital role of CLO-PIR in thrombotic- and bleeding-associated events has been recognized [10,11]. It is worth noting that the predictive power of CLO-PIR for postoperative hemorrhage in DAPT patients undergoing coronary artery bypass graft (CABG) and cardiovascular stent implantation is of great value as a guidance for subsequent management processes [11,12]. However, few reports have focused on the application of TEG-PM in the bleeding management of dental surgeries.

In this prospective study, a CLO-PIR of 75 % was used as the threshold for patients with normal and high responses to CLO [13]. The post-extraction clotting status of the two groups of patients was compared, and the effect of CLO-PIR was evaluated.

METHODS

This study was approved by the Research Ethics Committee of Shanghai Stomatological Hospital, Fudan University (approval no. 20190017), and was conducted in accordance with the guidelines of Declaration of Helsinki [7]. Written informed consent was obtained from all participants.

Patient enrolment

A total of ninety (90) patients on an uninterrupted maintenance dose of DAPT (ASA 100 mg/day and CLO 75 mg/day, age ≥40 years) were prospectively recruited for this study. They were scheduled for a single-tooth extraction at the Department of Oral and Maxillofacial Surgery, Shanghai Stomatological Hospital, Fudan University from June 2020 to December 2021.

Exclusion criteria

Patients with history of systemic bleeding disorders, chronic renal or hepatic disease, coagulopathies, epilepsy, debilitating respiratory diseases, long-term steroid use, chemotherapy, anticoagulants, single antiplatelet medications, alcoholism, or poorly controlled arterial hypertension (systolic > 150 mmHg; diastolic > 90 mmHg) were excluded. Patients with abnormal results in terms of blood routine test, activated partial thromboplastin time (APTT), prothrombin time (PT), or hyporesponsiveness to CLO (CLO-PIR ≤ 30 %) or ASA (ASA-PIR ≤ 50 %) were also excluded [9].

The participants were distributed into normal CLO-PIR (N-CLO-PIR, 30 % <CLO-PIR ≤75 %) and high CLO-PIR (H-CLO-PIR, CLO-PIR >75 %) groups [13]. In each group, the patients were further stratified into those with normal ASA-PIR (N-ASA-PIR, 50 % <ASA-PIR ≤75 %) and high ASA-PIR (H-ASA-PIR, ASA-PIR >75 %) for detailed comparisons [14].

Teeth including cracked teeth, residual roots and crowns were scheduled for extraction. Evaluation of extraction difficulty was performed based on two criteria: First, an elevator with narrow blade was used to locate the dento-alveolar space at the cervical region of a tooth. If the blade could be inserted into the space without much pressure, the tooth was considered eligible. Otherwise, the tooth was excluded due to the possible usage of aggressive methods. Second, a radiographic image of each tooth was obtained preoperatively. The tooth was considered eligible if the image showed the existing dark continuous lines (periodontal ligaments) between the root and alveolar bone. Teeth with missing dark continuous lines (ankylosed teeth) were excluded due to the high surgical complexity. Teeth that met the two criteria were selected. Furthermore, teeth with possible periodontitis (alveolar bone resorption shown by radiographic examination), or acute periodontal inflammation were excluded.

Pre-extraction TEG

Pre-extraction TEG was performed by the same protocol as described in our previous study [15]. The values of maximal amplitude (MA) in Kaolin-enhanced TEG and CLO-PIR, ASA-PIR, MA_{ADP} (MA induced by ADP) and MA_{AA} (MA induced by AA) in TEG-PM were recorded.

Surgical procedure

Regional block anesthesia with local infiltration was applied to the lower premolars and molars. For the lower anterior and upper teeth, local infiltration was performed (2 % lidocaine with a maximum of 5 mL) [15]. For a multiple-rooted tooth, the clinical crown was sectioned using a turbine handpiece. The following procedure was the same as that of the extraction of a single-rooted tooth. An elevator was used to achieve minor alveolar bone expansion and tooth luxation, and a forcep was used for subsequent delivery. Unnecessary tissue injury and intraoperative root fracture were avoided. The duration of the operation was recorded. The patients' history of disease and hematological findings remained unknown to the oral surgeon.

Surgical surface assessment

To explore the potential correlation between surgical surface and postoperative clotting, the surgical surface assessment was performed according to the alveolar surface of the tooth (incisors, canines and premolars, molars were recorded as 1, 1.5, 2 points respectively) [16].

Primary outcome and assessment of post-extraction clotting

The primary outcome was defined as complete intra-alveolar clot formation, and the clotting events were classified using a four-stage assessment [6]. Each patient received gauze pressure at the surgical site, and was observed at post-extraction 15 and 30 min. Occurrence of the primary outcome at 15 and 30 min was recorded as "normal clotting (15 min)" and "normal clotting (30 min)" [6]. In patients with continuous bleeding beyond 30 min, an absorbable gelatin sponge was applied in the socket and stabilized by suturing. Reexamination was conducted at 15 min intervals until a clot had completely formed. The primary outcome occurring under the additional hemostatic measures was classified as "prolonged bleeding" [6]. Continuous bleeding, that could not be controlled by local measures was identified as "severe bleeding" [2]. The patients' personal and medical information were restricted from the observer. Patients left the hospital until complete clot formation was achieved. The patients were followed up by telephone on the third and seventh days postoperatively.

Sample size determination

As studies targeting the effect of different CLO responsiveness on post-extraction clotting are rare, 30 patients on the maintenance dose of DAPT (15 with N-CLO-PIR and 15 with H-CLO-PIR) were enrolled in a pilot study. The results showed that 87 % (13/15) of the former and 60 % (9/15) of the latter exhibited normal clotting. The sample size was calculated using the proportion test of PASS (version 11, NCSS LLC, Kaysville, USA). A two-tailed hypothesis test and an alpha level of 0.05 were considered, with 85 % power, a sample size of 45 was used for each group.

Statistical analysis

SPSS (version 22.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Student *t*-test was used for intergroup comparisons of age, blood pressure, laboratory results, and surgical duration where/if continuous variables featured normal distribution. Or else, the Mann-Whitney *U* test was conducted. In terms of sex, smoking and diabetes history and surgical surface, chi-square test was conducted to find the statistical differences between the two groups. The Mann-Whitney *U* test was used to compare the clotting assessment results.

The independent predictive role of hematological data, surgical duration and surface on prolonged bleeding was investigated by odds ratios (OR) and 95 % confidence intervals (CI) in the univariate model of logistic regression. The effectiveness of CLO-PIR in distinguishing patients with prolonged bleeding was evaluated using receiver operating characteristic curve (ROC) analysis, while the Youden index was used to calculate the optimal cut-off value of CLO-PIR. Categorical and continuous variables are showed as numbers (n) and mean ± SD, respectively. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 90 DAPT patients with a mean age of 68.8 ± 9.2 years were enrolled, including 62 males and 28 females. As shown in Table 1, there were no significant intergroup differences regarding demographic characteristics, surgical details, results of blood routine or coagulation function tests. The TEG analysis also demonstrated that no statistical differences in

terms of MA, ASA-PIR, and MA_{AA} were observed. Besides, the CLO-PIRs were negatively correlated with the MA_{ADP} values in both groups. Although uncontrolled bleeding did not occur in either group, more patients in the N-CLO-PIR group presented with normal clotting (91.1 % vs. 75.6 %, $p < 0.001$), while the overall ASA-PIR was similar between the two groups.

Further comparison demonstrated that, in patients with N-ASA-PIR, the N-CLO-PIR group also showed a higher percentage of patients presented with normal clotting (90 % vs. 76.2 %, p=0.010). The results were consistent with those observed in patients with H-ASA-PIR (92 % vs. 75 %, p=0.013) (Table 2). However, in the N-CLO-PIR and H-CLO-PIR groups, the clotting results were similar in patients with N-ASA-PIR and H-ASA-PIR (Table 3). Accordingly, patients with prolonged bleeding had a higher CLO-PIR level than those with normal clotting (85.6 ± 15.5 vs. 70.0 ± 16.4, p=0.001), while the ASA-PIRs were comparable in the two groups of patients (77.9 ± 15.9 vs. 76.0 ± 14.3, p=0.661) (Table 4). Besides, no significant difference was observed in any comparisons regarding surgical duration and surgical surface (Tables 1-4).

The CLO-PIR remained an independent risk factor for prolonged bleeding (OR=1.071, 95 % CI: 1.024-1.120, p=0.003) after logistic regression analysis of the potential risk variables (Table 5). In the corresponding ROC analysis of CLO-PIR value, an area of 0.772 (p = 0.001) was obtained below the curve with a 95 % CI of 0.630-0.918. The optimal cut-off value was 92.9 %, with the sensitivity and specificity of 53.3 % and 96 %, respectively (Figure 1).

Table 1: Demographic and clinical characteristics, surgical details and clotting status in each of the two groups

Variable	N-CLO-PIR (n=45)	H-CLO-PIR (n=45)	*P*-value
Age (years)	70.0±8.4	67.6±9.9	0.284
Sex (Male/ Female)	27/18	35/10	0.110
Blood pressure (mmHg)			
Systolic	131.6±7.6	130.9±10.5	0.705
Diastolic	79.7±6.1	79.8±8.0	0.941
Smoking (Yes/No)	8/37	8/37	1.000
Diabetes (Yes/No)	4/41	6/39	0.739
Blood routine			
WBC (10^9/L)	6.28±1.35	6.03±1.75	0.436
RBC (10^{12}/L)	4.52±0.47	4.57±0.59	0.678
Hemoglobin (g/L)	138.2±14.6	141.7±14.5	0.252
PLT (10^9/L)	207.5±52.3	189.5±48.3	0.093
Coagulation function			
APTT (s)	27.1±3.6	26.3±2.8	0.263
PT (s)	11.5±0.6	11.4±0.6	0.883
TEG parameter			
MA (mm)	63.3±3.8	62.2±4.3	0.178
ASA-PIR (%)	78.0±15.8	77.2±15.6	0.793
MA_{AA} (mm)	24.3±10.5	24.5±9.9	0.909
CLO-PIR (%)	57.9±9.8	87.2±7.8	<0.001
MA_{ADP} (mm)	34.6±6.1	19.5±5.6	<0.001
Surgical duration (min)	2.8±1.9	3.4±3.0	0.249
Surgical surface			
1	8	2	0.147
1.5	12	13	
2	25	30	
Clotting assessment			
Normal clotting (15 min)	23	7	<0.001
Normal clotting (30 min)	18	27	
Prolonged bleeding	4	11	
Severe bleeding	0	0	

WBC: white blood cell (3.50-9.50 10^9/L); RBC: red blood cell (3.80-5.10 10^{12}/L); Hemoglobin (115-150 g/L); PLT, platelet (125-350 10^9/L); APTT: activated partial thromboplastin time (20-40 s); PT: prothrombin time (10-14 s); MA: maximum amplitude (50.00-70.00 mm); ASA-PIR, ASA inhibition rate using inducer arachidonic acid; MA_{AA}, maximum amplitude using inducer arachidonic acid; CLO-PIR: CLO inhibition rate using inducer adenosine diphosphate; MA_{ADP}, maximum amplitude using inducer adenosine diphosphate

Table 2: Intergroup comparison of hematological test results, surgical details and clotting status in DAPT patients with N-ASA-PIR or H-ASA-PIR

Parameter	N-CLO-PIR	H-CLO-PIR	*P*-value	N-CLO-PIR	H-CLO-PIR	*P*-value
	N-ASA-PIR			H-ASA-PIR		
	(n=20)	(n=21)		(n=25)	(n=24)	
Hematological data						
MA (mm)	63.9±3.9	61.4±4.8	0.076	62.9±3.7	62.8±3.7	0.980
CLO-PIR (%)	57.6±9.3	87.8±8.3	<0.001	58.2±10.5	86.5±7.4	<0.001
MA_{ADP} (mm)	36.3±5.1	20.2±5.4	<0.001	33.2±6.5	18.9±5.8	<0.001
PLT (10^9/L)	222±55	195±52	0.117	196±48	184±46	0.394
APTT (S)	26.5±3.0	27.0±2.5	0.593	27.5±4.0	25.8±2.9	0.081
PT (S)	11.4±0.6	11.5±0.6	0.652	11.5±0.7	11.4±0.7	0.559
Surgical duration (min)	2.5±1.3	2.9±2.2	0.517	3.1±2.3	3.9±3.5	0.619
Surgical surface						
1	4	1	0.353	4	2	0.842
1.5	5	5		7	8	
2	11	15		14	14	
Clotting assessment						
Normal clotting (15 min)	11	3	0.010	12	4	0.013
Normal clotting (30 min)	7	13		11	14	
Prolonged bleeding	2	5		2	6	
Severe bleeding	0	0		0	0	

MA: maximum amplitude (50.00-70.00 mm); CLO-PIR: CLO inhibition rate using inducer adenosine diphosphate; MA_{ADP}: maximum amplitude using inducer adenosine diphosphate; PLT: platelet (125 - 350 10^9/L); APTT: activated partial thromboplastin time (20 - 40 s); PT: prothrombin time (10 - 14 s)

Table 3: Intragroup comparisons of hematological test results, surgical details and clotting status between DAPT patients with N-ASA-PIR and H-ASA-PIR

Parameter	N-CLO-PIR		*P*-value	H-CLO-PIR		*P*-value
	N-ASA-PIR (n=20)	H-ASA-PIR (n=25)		N-ASA-PIR (n=21)	H-ASA-PIR (n=24)	
Hematological data						
MA (mm)	63.9±3.9	62.9±3.7	0.350	61.4±4.8	62.8±3.7	0.280
ASA-PIR (%)	62.8±8.1	90.3±7.6	<0.001	62.6±6.3	89.9±8.1	<0.001
MA_{AA} (mm)	33.8±6.3	16.7±5.9	<0.001	33.2±6.0	17.0±5.3	<0.001
PLT (10^9/L)	222±55	196±48	0.097	195±52	184±46	0.456
APTT (s)	26.5±3.0	27.5±4.0	0.337	27.0±2.5	25.8±3.0	0.148
PT (s)	11.4±0.6	11.5±0.7	0.794	11.5±0.6	11.4±0.7	0.445
Surgical duration (min)	2.5±1.3	3.1±2.3	0.303	2.9±2.2	3.9±3.5	0.374
Surgical surface						
1	4	4	1.000	1	2	0.709
1.5	5	7		5	8	
2	11	14		15	14	
Clotting assessment						
Normal clotting (15 min)	11	12	0.731	3	4	0.959
Normal clotting (30 min)	7	11		13	14	
Prolonged bleeding	2	2		5	6	
Severe bleeding	0	0		0	0	

MA: maximum amplitude (50.0 -70.0 mm); ASA-PIR: ASA inhibition rate using inducer arachidonic acid; MA_{AA}: maximum amplitude using inducer arachidonic acid; PLT: platelet (125 - 350 10^9/L); APTT: activated partial thromboplastin time (20-40 sec); PT: prothrombin time (10 - 14 s)

Table 4: Demographic and clinical characteristics, hematological test results, surgical details of DAPT patients with normal clotting and prolonged bleeding

Parameter	Normal clotting (n=75)	Prolonged bleeding (n=15)	*P*-value
Age (Years)	68.7±9.3	70.0±8.6	0.477
Sex (Male/Female)	50/25	12/3	0.375
Blood pressure (mmHg)			
Systolic	130.9±8.7	133.1±11.0	0.396
Diastolic	79.5±7.0	81.1±7.5	0.421
Diabetes (Yes/ No)	8/ 67	2/ 13	0.671
Hematological data			
MA (mm)	63.0±3.9	61.5±4.6	0.398
ASA-PIR (%)	77.9±15.9	76.0±14.3	0.661
MA_{AA}	23.6±9.9	28.4±10.6	0.398
CLO-PIR (%)	70.0±16.4	85.6±15.5	0.001
MA_{ADP}	27.9±9.4	22.8±9.7	0.060
PLT (10^9/L)	202±51	183±51	0.206
APTT (s)	26.6±3.1	27.1±3.8	0.626
PT (s)	11.4±0.6	11.6±0.8	0.443
Surgical duration (min)	2.9±2.3	4.0±3.5	0.234
Surgical surface			
1	9	1	0.072
1.5	24	1	
2	42	13	

MA: maximum amplitude (50.0 - 70.0 mm); ASA-PIR: ASA inhibition rate using inducer arachidonic acid; MA_{AA}: maximum amplitude using inducer arachidonic acid; CLO-PIR: CLO inhibition rate using inducer adenosine diphosphate; $MA_{ADP:}$ maximum amplitude using inducer adenosine diphosphate; PLT, platelet (125 - 350 10^9/L); APTT: activated partial thromboplastin time (20 - 40 s); PT: prothrombin time (10 - 14 s)

Table 5: Predictive power of variables for prolonged bleeding using univariate logistic regression analysis

Predictor	OR	(95% CI)	*P*-value
Surgical duration	1.137	(0.948-1.363)	0.166
Surgical surface			0.128
1 vs. 1.5	0.375	(0.021-6.652)	0.504
1 vs. 2	0.359	(0.041-3.105)	0.352
1.5 vs. 2	0.135	(0.017-1.094)	0.061
Hematological data			
PLT	0.993	(0.981-1.004)	0.206
PT	1.410	(0.590-3.369)	0.439
APTT	1.044	(0.879-1.242)	0.622
MA	0.913	(0.797-1.045)	0.188
ASA-PIR (%)	0.992	(0.957-1.028)	0.668
CLO-PIR (%)	1.071	(1.024-1.120)	0.003

PLT: platelet; PT: prothrombin time; APTT: activated partial thromboplastin time; MA: maximum amplitude (50.0 - 70.0 mm); ASA-PIR: ASA inhibition rate using inducer AA; CLO-PIR: CLO inhibition rate using inducer ADP

Follow-up phone calls revealed that 3 - 4 patients in N-CLO-PIR and H-CLO-PIR groups experienced mild bleeding in the first week post-operation, respectively, which occurred when they were chewing. Ideal hemostatic effects were achieved after the patients pressed the wounds using sterile cotton balls. In view of this, it was believed that the occurrence of bleeding was related to the eating habits and behaviors of patients rather than the effects of DAPT.

DISCUSSION

The CLO is an ADP receptor (P2Y12) antagonist that inhibits platelet aggregation and crosslinks with fibrin [4]. Owing to the intensified effect of CLO addition to ASA, DAPT has been recommended for the prevention of recurrent thrombotic events [1]. Although pre-extraction DAPT continuation has been advised in some guidelines [4], the exact correlation between patients' response to DAPT and postoperative clotting remains unclear.

Although PT and APTT are commonly performed in DAPT patients to ensure the safety of dental extraction, the value of such practices may be limited as these tests do not specifically target platelet function. Moreover, light transmittance aggregometry (LTA) is widely used to measure patients' response to antiplatelet treatments.

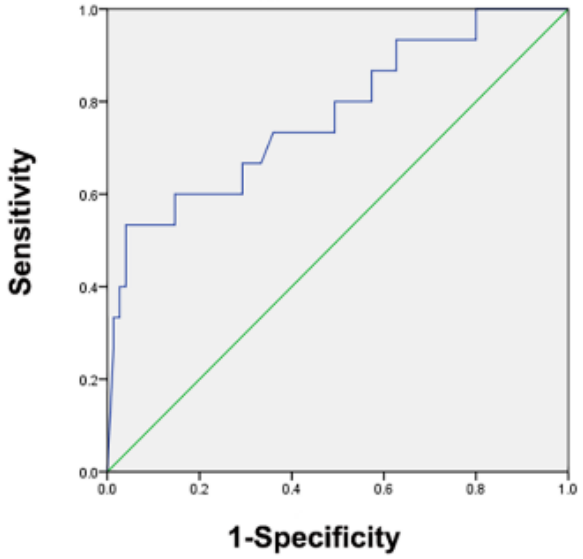

Figure 1: ROC analysis of CLO-PIR for prolonged post-extraction bleeding. An area of 0.772 with a p value of 0.001 was obtained below the curve, with a 95 % CI of 0.630 to 0.918. The optimal cut-off value calculated as the Youden index was 92.9 %, with sensitivity and specificity of 53.3 % and 96 %, respectively. However, a cut-off value of 78.6 % was selected, with a sensitivity and specificity of 73.3 and 64 %, respectively, to meet clinical requirements better

However, LTA has the disadvantages of limited reproducibility, time consumption and low specificity for P2Y12 channels [10,17]. Currently, TEG-PM is a new method of evaluating platelet aggregation [8], and has advantages over LTA with respect to testing comprehensiveness, reproducibility of results and convenience of clinical usage [10]. Given the reliability of TEG-PM in monitoring drug efficacy and guiding individualized antiplatelet regimens [8,17], the application of the instrument was appropriate in this study.

In view of the similarity in demographic characteristics, surgical details, function of the extrinsic and intrinsic coagulation pathways between the two groups, it was concluded that the different clotting results were mainly associated with the patients' response to DAPT. Uncontrolled bleeding was not observed in any patient, which is consistent with the results of previous studies indicating the feasibility of pre-extraction DAPT continuation [1-3,18].

The percentage of patients that showed normal clotting in the N-CLO-PIR was higher than that in the H-CLO-PIR group, while the overall ASA-PIR of the two groups was similar. The result was similar to that observed in patients with N-ASA-PIR and H-ASA-PIR. As the increase in CLO-PIR significantly prolonged the bleeding time regardless of the ASA-PIR level, the post-extraction clotting may be mainly affected by the patients' CLO responsiveness. In contrast, in N-CLO-PIR and H-CLO-PIR groups, the intra-group comparison of revealed similar clotting status of patients with N-ASA-PIR and H-ASA-PIR, suggesting that the increase in ASA responsiveness may exert an unobvious influence at a certain CLO-PIR level. these results preliminarily demonstrate the prominence of the CLO antiplatelet effect in slowing the post-extraction clotting process in DAPT patients, especially when CLO-PIR is above 75 %. This finding was supported by the higher CLO-PIR and similar ASA-PIR values of patients with prolonged bleeding when compared with those exhibiting normal clotting. It is worth mentioning that the negative correlation between the PIR and corresponding MA values validated the credibility of patients' DAPT responsiveness in the present study.

Postoperative prolonged bleeding of DAPT patients is multifactorial, and CLO-PIR remained an independent risk factor after logistic regression analysis. However, the present result is contradictory to those of previous studies using PFA-100 and VerifyNow, in which the correlation between the effect of CLO and post-extraction bleeding was not clarified [18,19]. In view of this, PFA-100 and VerifyNow are not highly efficient indicators of CLO responsiveness [17,20], and the aggressive extraction approach or strong hemostatic measures adopted in previous studies could mask the effect of CLO. Hence, TEG-PM was used to try to minimize such interference factors in this study, and a non-surgical extraction was performed on each patient to avoid an increase in bleeding caused by excessive trauma. In addition, the anesthetic did not contain epinephrine, nor did the gauze contain hemostatic agents, which also contributed to the objective insight into the effects of CLO on intra-alveolar clotting.

The results indicated that the optimal cut-off value of CLO-PIR in distinguishing patients with prolonged bleeding was 92.9 %, with a sensitivity of 53.3 % and specificity of 96 %. However, considering the value may lead to a high rate of missed diagnoses in patients with a high risk of postoperative bleeding, CLO-PIR of 78.6 % was selected with a sensitivity and specificity of 73.3 % and 64.0 %, to better meet the clinical requirement.

This study has several limitations. First, the conclusions should not be extended to patients with a history of antiplatelet treatments in higher doses, bleeding disorders, coagulopathies, or patients undergoing aggressive dental

procedures. Second, the statistical power of CLO-PIR is sufficient as an independent predictor of prolonged bleeding. The limited sample size still revealed the preliminary nature of the study. Thus, prospective studies including more eligible patients should be carried out in the future to acquire more sufficient clinical evidence.

CONCLUSION

In patients receiving a maintenance dose of DAPT, a high platelet inhibitory response to CLO may prolong the clotting process after dental extraction. Moreover, CLO-PIR in TEG-PM may serve as an effective indicator for the discrimination of prolonged bleeding (>30 min), with a CLO-PIR of 78.6 % as the cut-off point. These findings may help to avoid the unnecessary use of DAPT suspension or postponement of operation in DAPT patients scheduled for dental extractions.

DECLARATIONS

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Ethical approval

This study was approved by the Research Ethics Committee of Shanghai Stomatological Hospital, Fudan University (approval no. 20190017).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yaqiong Zhang and Yijie Zhao collected the data and drafted part of the manuscript; Meng Wang and Jiaqi Wang helped in the acquisition of the data and performed data analysis; Mengmeng Lu and Zhicheng Yang designed the study and revised the manuscript.

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