ภาวะแทรกซ้อนภายหลังการทำศัลยกรรมขนาดเล็กในช่องปากในผู้ป่วยที่รับยาต้านการเกิดลิ่มเลือดชนิดรับประทาน

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบอัตราการเกิดภาวะเลือดออก และอัตราการเกิดภาวะแทรกซ้อนทางระบบจากการทำศัลยกรรมขนาดเล็กในช่องปาก ระหว่างผู้ป่วยที่หยุดยาและไม่หยุดยาต้านการเกิดลิ่มเลือด

วัสดุอุปกรณ์และวิธีการ: การศึกษาเชิงสังเกตการณ์แบบย้อนหลังจากเวชระเบียนผู้ป่วยที่โรงพยาบาลตากสิน ระหว่าง มกราคม 2560 ถึง ธันวาคม 2561 โดยบันทึกข้อมูลในผู้ป่วยที่เข้าทำศัลยกรรมขนาดเล็กในช่องปาก และมีประวัติการหยุดยา หรือไม่หยุดยาต้านการเกิดลิ่มเลือด ก่อนทำหัตถการ และมีข้อมูลติดตามการเกิดภาวะแทรกซ้อนหลังทำหัตถการ ได้แก่ ภาวะเลือดออก และโรคกล้ามเนื้อหัวใจขาดเลือด หรือโรคหลอดเลือดสมอง

ผลการทดลอง: จำนวนผู้ป่วย ทั้งหมด 574 คน มีอายุเฉลี่ย 66.89 ± 10.63 ปี และร้อยละ 54.20 เป็นเพศชาย ผู้ป่วยส่วนใหญ่มีประวัติเป็นโรคความดันโลหิตสูง (ร้อยละ 68.30) โรคเบาหวานชนิดที่ 2 (ร้อยละ 48.60) ใช้ยาแอสไพรินเดี่ยว (ร้อยละ 77.40) เข้ารับการถอนฟัน (ร้อยละ 92.70) และหยุดยาต้านการเกิดลิ่มเลือดก่อนทำหัตถการ (ร้อยละ 54.18) ผลการวิเคราะห์พบว่า ผู้ป่วยที่ไม่หยุดยาต้านการเกิดลิ่มเลือดมีอุบัติการณ์เกิดภาวะเลือดออกหลังทำหัตถการใกล้เคียงกับผู้ป่วยที่หยุดยาต้านการเกิดลิ่มเลือด (ร้อยละ 1.14 และ 1.29 ตามลำดับ) และมีค่า adjusted OR เท่ากับ 0.446 (95% CI 0.080-2.494 และ p = 0.358) ในทางกลับกัน พบว่า ผู้ป่วยที่หยุดยาต้านการเกิดลิ่มเลือดมีแนวโน้มเล็กน้อยต่อการเกิดภาวะแทรกซ้อนทางระบบ หลังการทำหัตถการ มากกว่าผู้ป่วยที่ไม่หยุดยาต้านการเกิดลิ่มเลือด (ร้อยละ 2.57 และ 1.90 ตามลำดับ) และมีค่า adjusted OR เท่ากับ 1.422 (95% CI 0.454–4.452 และ p = 0.545)

สรุป: การไม่หยุดยาต้านการเกิดลิ่มเลือดไม่เพิ่มความเสี่ยงต่อการเกิดภาวะเลือดออกหลังการทำหัตถการ อย่างไรก็ตาม การหยุดยาต้านการเกิดลิ่มเลือดอาจเพิ่มความเสี่ยงต่อการเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือด ดังนั้น ควรประเมินความเสี่ยงและประโยชน์ของผู้ป่วยแต่ละรายอย่างรอบคอบก่อนพิจารณาการหยุดยาต้านการเกิดลิ่มเลือดก่อนทำหัตถการ

คำสำคัญ: ยาต้านการเกิดลิ่มเลือด ยาต้านการแข็งตัวของเลือด ยาต้านเกล็ดเลือด ศัลยกรรมขนาดเล็กในช่องปาก ภาวะลิ่มเลือดอุดตันในหลอดเลือด ภาวะแทรกซ้อนทางระบบ

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Postoperative Complications from Oral Minor Surgery in Patients on Oral Antithrombotic Drugs

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Abstract

Objectives: To compare of bleedings and systemic complications after minor oral surgery between patients with interrupted antithrombotic drugs (IAT) and continued antithrombotic drugs (CAT)

Materials and Methods: An observational retrospective cohort study retrieved from patient medical records at Taksin hospital between January 2017 to December 2018. Data were collected from patients who underwent oral minor surgery with a history of IAT or CAT perioperatively. Post-operative complications including bleeding, myocardial infarction, and stroke, were evaluated.

Results: A total of 574 patients, (54.2% male) with mean age of 66.89 ± 10.63 years old. were included. In general, there were patients with hypertension (68.30%), type 2 diabetes mellitus (48.60%), aspirin monotherapy (77.40%), dental extraction (92.70%) and IAT (54.18%). The results showed that patients in the CAT group had a similar incidence of post-operative bleedings to the IAT group (1.14 vs. 1.29%, respectively) with an adjusted OR of 0.446 (95% CI 0.080–2.494, p = 0.358). In contrast, the IAT group had a slight trend without statistical significance towards post-operative systemic complications compared with CAT group (2.57 vs. 1.90%, respectively) with an adjusted OR of 1.422 (95% CI 0.454–4.452, p = 0.545).

Conclusions: Continuing the antithrombotic drugs did not increase the post-operative bleeding risk. However, interrupting the antithrombotic drugs may influence the risk of systemic complications. Therefore, any individual patient should be carefully assessed for the risks and benefits of antithrombotic drugs before consideration of perioperative antithrombotic interruption.

Keywords: antithrombotic drug, anticoagulants, antiplatelets, oral minor surgery, thromboembolism, systemic complication

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Introduction

Due to increasing life expectancy, patients who are taking oral antithrombotic drugs for prevention of cardiovascular events and undergoing dental extraction have been increased. Dental providers must consider the actual risks of post-operative bleedings and thromboembolic complications from any potential interaction between oral minor surgery and antithrombotic therapy. This is a dilemma for dental providers whether to continue or discontinue antithrombotic drugs perioperatively and what is the best decision-making process.

Aspirin (acetylsalicylic acid; ASA) is a nonsteroidal anti-inflammatory drug (NSAIDs). It also has an antiplatelet activity by inhibiting platelet aggregation that induced from thromboxane A2. Based on this function, it is indicated for primary or secondary prevention of cardiovascular diseases.(1,2) Clopidogrel is an antiplatelet drug that irreversibly binds to platelet purinergic P2Y12 receptor which is activated by adenosine diphosphate (ADP). Like ASA, clopidogrel is indicated mainly for secondary prevention of atherothrombotic diseases. (3) Warfarin, an oral vitamin K antagonist (VKA), prolongs prothrombin time by antagonizing the vitamin K-dependent clotting factors (II, VII, IX, X). (4) Warfarin is the most common oral anticoagulant used for prevention and treatment of thromboembolisms, such as atrial fibrillation, mechanical heart valve, and venous thromboembolism. (5,6)

The dental procedure is classified under a minor surgery, which the risk of thromboembolisms associated with discontinuation of the antithrombotic drugs is low and the risk of bleedings is far out-weight when continuing the antithrombotic drugs. (7-12) Warfarin has a long half-life of 48 to 72 hours and a delay-onset of 76 to 96 hours after cessation as well as re-initiation of the treatment. (13-21) Dual antiplatelet (DAPT) combined of low-dose ASA and one P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel), which is recommended as a first-line treatment for secondary prevention in patients with coronary artery disease. (22,23) There are studies in dental procedures concluded that the risk of thromboembolic events from discontinuation of ASA or DAPT is more harm than the risk of post-operative bleedings from the continuation of antiplatelets. (10,11) Additionally, discontinuation of ASA or DAPT particularly clopidogrel is not recommended in the setting of dental procedures. (24,25)

This study aimed to compare the incidences of post-operative complications including bleedings and systemic complications between patients with interrupted antithrombotic drugs and continued antithrombotic drugs.

Materials and methods

Study design and population:

We conducted an observational retrospective cohort study by retrieving data from electronic medical records of all patients who aged at least 18 years old, underwent minor oral surgery, and received oral antithrombotic drugs between January 2017 to December 2018 at Taksin hospital. The study protocol was approved by the Bangkok metropolitan administration human research ethic committee (BMAHREC) No.S007h/63 22 May 2020. Patients were categorized into two groups as interrupted antithrombotic drug

(IAT) groups as and continued antithrombotic drug (CAT) group. Antithrombotic drugs in this study included antiplatelets (ASA or clopidogrel), or anticoagulant (warfarin). The IAT group referred to patients with discontinuation of an antithrombotic drug at least 3 days before minor oral surgery for ASA or clopidogrel, or at least 1 day for warfarin. The CAT group referred to patients with continuation of ASA, clopidogrel, or warfarin before and on the day of minor oral surgery without any interruption. The minor oral surgery was defined as tooth extraction, surgical removal, and torectomy. All patients were given a post-operative self-care instruction by continuing to bite on the gauze pack for 1 hour to stop bleeding and taking good care of oral hygiene. In the case of patients on warfarin, surgical wounds were applied with local hemostatic agents, such as oxidized regenerated cellulose, and sutured with silk 3-0.

Outcomes:

Primary outcome was frequency of post-operative bleeding defined as any level of bleedings that occurred immediately after surgical procedures or up to 3 days after surgery. Bleeding definition and classification were modified from the bleeding academic research consortium (BARC) (26,27), as followed: Level 1 is any bleeding that stopped spontaneously without any additional treatment; Level 2 is any bleeding that required additional treatment by a health care professional with materials or tools, such as stitches to stop the bleed within 10 minutes on an observation; Level 3 is any overt bleeding that required additional wound suture with hospitalization for blood transfusion and intravenous fluid resuscitation. Secondary outcomes were systemic complication events including myocardial infarction or stroke that occurred after dental surgery within 30 days or longer.

Statistical analysis:

The baseline characteristics of patients with IAT and CAT were analyzed using the independent student t-test for continuous variables and the Chi-square test for categorical variables. Multiple logistic regression was conducted for comparing the risk of bleedings or systemic complications after surgery between two groups and calculated for odds ratio (OR) with 95% confidence intervals at alpha value of 0.05 (two-sided). Potential covariates were controlled in the models, such as age, sex, medical history, dental procedures, antithrombotic drugs. All the analyses were performed by a statistical computer software.

Results

Patients:

A total of 574 patients were identified with a history of minor oral surgery and a prescription of antithrombotic drugs. Followed-up data of post-operative complications were available for all patients. Antithrombotic drugs uses were categorized as IAT group in 54.18%, and CAT group in 45.82% of patients. The characteristics of age, sex, medical history, antithrombotic drug regimens with warfarin dose, international normalized ratio (INR), and dental procedures are shown in table 1.

Table 1. Patient Characteristics at Baseline.

Characteristics	Total (n = 574)	IAT (n = 311)	CAT (n = 263)	p-value
Age – year (mean ± SD)*	66.89 ± 10.63	66.70 ± 10.88	67.11 ± 10.34	0.640
Male sex – no. (%)†	311 (54.20)	164 (52.70)	147 (55.90)	0.449
Medical history – no. (%)†				
Type 2 diabetes mellitus	279 (48.60)	147 (47.30)	132 (50.20)	0.485
Hypertension	392 (68.30)	211 (67.80)	181 (68.80)	0.802
Coronary artery disease	123 (21.40)	72 (23.20)	51 (19.40)	0.274
Stroke	117 (20.40)	64 (20.60)	53 (20.20)	0.899
Atrial fibrillation	45 (7.80)	27 (8.70)	18 (6.80)	0.414
Heart valve disease	18 (3.10)	10 (3.20)	8 (3.00)	0.905
Hyperlipidemia	217 (37.80)	100 (32.20)	117 (44.50)	0.002
Renal failure	41 (7.10)	25 (8.00)	16 (6.10)	0.365
Neurologic disease	109 (19.00)	60 (19.30)	49 (18.50)	0.840
Antithromboticregimens – no. (%)†				
Aspirin	444 (77.40)	246 (79.10)	198 (75.30)	0.277
Clopidogrel	25 (4.40)	14 (4.50)	11 (4.20)	0.852
Warfarin	71 (12.40)	35 (11.30)	36 (13.70)	0.377
Aspirin + Clopidogrel	25 (4.40)	8 (2.60)	17 (6.50)	0.023
Aspirin + Warfarin	9 (1.60)	8 (2.60)	1 (1.40)	0.035
Warfarin (n = 80)*				
Dose (mg/week) - mean ± SD	20.21 ± 9.50	22.47 ± 9.84	16.92 ± 8.07	0.021
INR - mean ± SD	2.07 ± 0.86	2.05 ± 0.84	2.10 ± 0.90	0.800
Dental procedures – no. (%)†				
Tooth extraction	532 (92.70)	285 (91.60)	249 (93.90)	0.297
Surgical removal	2 (0.30)	1 (0.30)	1 (0.40)	0.905
Torectomy	43 (7.50)	27 (8.70)	16 (6.10)	0.234

IAT: interrupted antithrombotic drugs; CAT: continued antithrombotic drugs; SD: standard deviation; no.: number of patients; INR: international normalized ratio; N/A: not available; *Independent t-test; †Chi-Square test.

The total mean age was 66.89 ± 10.63 years old, which was similar to the both groups (p = 0.640). Almost half of patients were male in both groups (p = 0.449). A significantly higher proportion of patients with CAT had hyperlipidemia (p = 0.002). Antithrombotic regimens seemed to be similar in both groups. There were slightly more patients in the CAT group had ASA combined with clopidogrel (p = 0.023), although the IAT group had a slightly higher proportion of ASA combined with warfarin (p = 0.035). Warfarin was prescribed in 80 patients (13.94%), 43 patients were in the IAT group and 37 patients were in the CAT group. In addition, the mean warfarin weekly dose in the IAT group was higher than the CAT group with a statistical difference (22.47 ± 9.84 vs. 16.92 ± 8.07 mg/week, respectively, p = 0.021). However, the mean INR was comparable between IAT and CAT groups (2.05 ± 0.84 and 2.10 ± 0.90, respectively, p = 0.800). More than 90 percent of patients in both groups had tooth extraction. There were similar proportions of patients in the both groups underwent surgical removal or torectomy.

Outcomes:

The Incidence of postoperative bleedings was reported in 7 patients (1.20%) as shown in table 2. Comparison of post-operative bleedings between the IAT and CAT groups was analyzed by using the Chi-square test. The result revealed no statistically significant difference between the IAT and the CAT groups [4/311 (1.29%) vs. 3/263 (1.14%), respectively, p = 0.874]. However, there was a trend for more pronounced post-opertaive bleedings in patients who interrupted warfarin (4/80 patients, 5.00%) than continued warfarin (2/80 patients, 2.50%), and continued antiplatelets (1/503 patients, 0.20%), respectively. The most frequent bleedings were classified in level 2 (4/7 patients), 2 patients interrupted warfarin, 1 patient continued warfarin, and another patient continued antiplatelets. All patients who experienced post-operative bleedings were received re-sutured and packed with surgicel. There were 2 patients who had bleedings in level 3 and were admitted into the hospital and given additional treatments with transamine mouth rinse and wound stenting. Additionally, there was 1 patient who continued warfarin and had an INR level of 2.00 before undergoing torectomy, experienced bleeding level 2 that was successfully managed by re-sutured, packed with surgicel, and transamine mouth rinse.

Incidence of total systemic complications after minor oral surgery was 2.26% (13/574). The incidence of stroke (7/574, 1.22%) and myocardial infarction (6/574, 1.05%) were similar as shown in table 2. All systemic complication events found in patients who were taking antiplatelets. The incidence of systemic complications in patients who interrupted antiplatelets compared with patients who continued antiplatelets was not statistically significant [8/503 (1.59%) vs. 5/503 (0.99%), respectively, p = 0.625]. The incidence of myocardial infarction in patients who interrupted antiplatelets was low, yet tended to be higher than patients who continued antiplatelets without statistically significant difference [4/503 (0.80%) vs. 2/503 (0.40%), respectively, p = 0.695]. The comparison of stroke events between patients who interrupted and continued antiplatelets was similar without statistical significance [4/503 patients (0.80%) vs. 3/503 patients (0.60%), respectively, p = 1.000]. For time to systemic complication events, mostly occurred in duration of longer than 30 days after minor oral surgery. The systemic complications that occurred within 30 days after procedure were myocardial infarctions which were recorded from 2 patients, one patient interrupted antiplatelets and another patient continued antiplatelets.

Table 2. Incidence of Post-operative Complications and Antithrombotic Drugs.

Post-operative Complications	Total (n = 574)	Aspirin or Clopidogrel (n = 503)			Warfarin (n = 80)		
		Interrupted	Continued	p-value	Interrupted	Continued	p-value
Bleedings – no. (%)*	7 (1.20)	0	1 (0.20)	0.451	4 (5.00)	2 (2.50)	0.681
Bleeding level – no. (%)*†				0.451			0.776
Level 1	1 (0.20)	0	0		1 (1.25)	0	
Level 2	4 (0.70)	0	1 (0.20)		2 (2.50)	1 (1.25)	
Level 3	2 (0.35)	0	0		1 (1.25)	1 (1.25)	
Dental procedures – no. (%)*							
Tooth extraction	6 (1.05)	0	1 (0.20)	N/A	4 (5.00)	1 (1.25)	0.333
Surgical removal	0	0	0	N/A	0	0	N/A
Torectomy	1 (0.20)	0	0	N/A	0	1 (1.25)	0.333
Bleeding Management*– no. (%)*	7 (1.22)	0	1 (0.20)	0.451	4 (5.00)	2 (2.50)	0.681
Re-sutured	7 (1.22)	0	1 (0.20)	0.451	4 (5.00)	2 (2.50)	0.509
Pack with surgicel	2 (0.35)	0	0	N/A	1 (1.25)	1 (1.25)	1.000
Transamine mouth rinse	2 (0.35)	0	0	N/A	1 (1.25)	1 (1.25)	1.000
Systemic Complications – no. (%)*	13 (2.26)	8 (1.59)	5 (0.99)	0.625	0	0	N/A
Myocardial infarction – no. (%)*	6 (1.05)	4 (0.80)	2 (0.40)	0.695	0	0	N/A
After procedure < 30 days	2 (0.35)	1 (0.20)	1 (0.20)	0.713	0	0	N/A
After procedure > 30 days	4 (0.70)	3 (0.60)	1 (0.20)		0	0	N/A
Stroke – no. (%)*	7 (1.22)	4 (0.80)	3 (0.60)	1.000	0	0	N/A
After procedure < 30 days	0	0	0	1.000	0	0	N/A
After procedure > 30 days	6 (1.05)	3 (0.60)	3 (0.60)		0	0	N/A
Unknown	1 (0.20)	1 (0.20)	0		0	0	N/A

no.: number of patients; N/A: not available; *Chi-Square test or Fisher's Exact test as appropriate; †Postoperative bleeding level – level 1 is bleeding that stopped spontaneously without any additional treatment; Level 2 is bleeding that required additional treatment by a health care professional with materials or tools such as stitches to stop the bleed within 10 minutes observation; Level 3 is overt bleeding that required additional wound suture with hospitalization for blood transfusion and intravenous fluid resuscitation.

In the table 3 showed multivariate analysis of post-operative complications. Results found that the CAT group was not associated with an increased risk of bleedings after minor oral surgery (adjusted OR 0.446, 95% CI 0.808–2.494, p = 0.358). In contrast, the IAT group had a small trend of increased systemic complications without statistical significance (adjusted OR 1.422, 95% CI 0.454–4.452, p = 0.545). Similarly, the systemic complication risks in patients with IAT had small trends without statistical significances to increase myocardial infarction (adjusted OR 1.583, 95%CI 0.279–8.986, p = 0.604), and stroke (adjusted OR 1.241, 95%CI 0.265–5.814, p = 0.784).

Table 3. Multivariable Analysis for Post-operative Complications.

Post-operative Complications	No. (%)	OR* (95% CI)	Adjusted OR† (95% CI)	p-value
Bleedings				
Total (n = 574)	7 (1.20)			
Interrupted (n = 311)	4 (1.29)	1.129 (0.250 – 5.091)	1.227 (0.213 – 7.058)	0.819
Continued (n = 263)	3 (1.14)	0.886 (0.196 – 3.993)	0.446 (0.080 – 2.494)	0.358
Systemic complications				
Total (n = 574)	13 (2.26)			
Interrupted (n = 311)	8 (2.57)	1.362 (0.440 – 4.216)	1.422 (0.454 – 4.452)	0.545
Continued (n = 263)	5 (1.90)	0.734 (0.237 – 2.271)	0.682 (0.218 – 2.138)	0.511
Myocardial infarction				
Total (n = 574)	6 (1.05)			
Interrupted (n = 311)	4 (1.29)	1.700 (0.309 – 9.358)	1.583 (0.279 – 8.986)	0.604
Continued (n = 263)	2 (0.76)	0.588 (0.107 – 3.237)	0.597 (0.104 – 3.425)	0.563
Stroke				
Total (n = 574)	7 (1.20)			
Interrupted (n = 311)	4 (1.32)	1.129 (0.250 – 5.091)	1.241 (0.265 – 5.814)	0.784
Continued (n = 263)	3 (1.14)	0.886 (0.196 – 3.993)	0.815 (0.172 – 3.865)	0.797

No.: number of patients; OR: odds ratio; CI: confidence interval; *simple logistic regression; †Multiple logistic regression with adjusted for antithrombotic drugs, dental procedures, age, sex, and medical history.

Univariate analysis of post-operative bleedings as shown in table 4. The analyses demonstrated that warfarin was a statistically significant risk factor that associated with increased post-operative bleedings (OR 46.338, 95% CI 5.492-390.990, p < 0.001), which was stronger than ASA (OR 0.471, 95% CI 0.006 - 0.391, p = 0.005). Interestingly, atrial fibrillation demonstrated astatistically significant association with increased post-operative bleedings (OR 9.375, 95% CI 2.031-43.277, p = 0.004). This result might be influenced by the highly frequent warfarin use for atrial filbrillation. There were 3 post-operative bleeding events from patients with atrial fibrillation and taking warfarin. Overall, the INR levels revealed no statistically significant association with post-operative bleedings. However, when compared with INR in subtherapeutic levels of less or equal to 1.99 as reference, the INR levels in therapeutic ranges of 2.00 to 2.49 seemed to have a slightly higher risk of post-operative bleedings without statistical siginificance (OR 6.643, 95% CI 0.634–69.621, p = 0.114) than the INR in supratherapeutic levels of higher or equal to 3.00 (OR 6.200, 95% CI 0.332-115.918, p = 0.222), and the INR in therapeutic levels of 2.50 to 2.99 (OR 2.385, 95% CI 0.138-41.079, p = 0.550), respectively. In addition, comorbid conditions that found no association with post-operative bleedings included heart valve disease, hyperlipidemia, and chronic kidney disease.

Table 4. Univariate Analysis for Post-operative Bleedings.

Risk Factors	Bleeding (n = 7)	No Bleeding (n = 567)	OR† (95% CI)	p-value
Continued antithrombotic drug – no. (%)	3 (42.86)	260 (45.86)	0.886 (0.196–0.993)	0.874
ASA	1 (14.29)			
Warfarin	2 (28.57)			
Dental procedures – no. (%)				
Tooth extraction	6 (85.71)	526 (92.77)	0.468 (0.055–3.978)	0.487
Surgical removal	0	2 (100.00)	N/A	N/A
Torectomy	1 (14.29)	42 (7.42)	2.079 (0.245–17.677)	0.503
Antithrombotic regimens – no. (%)				
Aspirin	1 (14.29)	443 (78.13)	0.471 (0.006–0.391)	0.005
Clopidogrel	0	25 (4.41)	N/A	N/A
Warfarin	6 (85.71)	65 (11.46)	46.338 (5.492–390.990)	< 0.001
Aspirin + Clopidogrel	0	25 (4.41)	N/A	N/A

Table 4. (cont.)

Risk Factors	Bleeding (n = 7)	No Bleeding (n = 567)	OR† (95% CI)	p-value
Warfarin	(n = 6)	(n = 63)		
INR - mean ± SD	2.55 ± 1.39	2.02 ± 0.79	1.819 (0.783–4.229)	0.164
INR level – no. (%)				
<1.99	1 (16.67)	31 (49.21)	reference	
2.00 – 2.49	3 (50.00)	14 (22.22)	6.643 (0.634–69.621)	0.114
2.50 – 2.99	1 (16.67)	13 (20.63)	2.385 (0.138–41.079)	0.550
> 3.00	1 (16.67)	5 (7.94)	6.200 (0.332–115.918)	0.222
Warfarin dose (mg/week) - mean ± SD	20.60 ± 10.99	20.16 ± 9.46	1.005 (0.913–1.106)	0.923
Age – year (mean ± SD)	63.57 ± 7.09	66.93 ± 10.66	0.973 (0.914–1.037)	0.402
Male sex – no. (%)	5 (71.43)	306 (53.97)	0.469 (0.090–2.437)	0.368
Medical history – no. (%)				
Type 2 diabetes mellitus	1 (14.29)	278 (49.03)	0.173 (0.021–1.448)	0.106
Hypertension	3 (42.86)	389 (68.61)	0.343 (0.076–1.550)	0.164
Coronary artery disease	1 (14.29)	122 (21.52)	0.608 (0.073–5.098)	0.646
Stroke	0	117 (20.63)	N/A	N/A
Atrial fibrillation	3 (42.86)	42 (7.41)	9.375 (2.031–43.277)	0.004
Heart valve disease	1 (14.29)	17 (3.00)	5.392 (0.615–47.289)	0.128
Hyperlipidemia	4 (57.14)	213 (37.57)	2.216 (0.491–9.997)	0.301
Chronic kidney disease	1 (14.29)	40 (7.05)	2.196 (0.258–18.687)	0.472
Neurologic disease	1 (14.29)	108 (19.05)	0.708 (0.084–5.945)	0.751

OR: odds ratio; CI: confidence interval; no.: number of patients; INR: international normalized ratio; SD: standard deviation; reference: bleeding events from patients with INR < 1.99 (the lowest range) was set as a comparator when calculated OR for the higher INR levels; N/A: not available; †simple logistic regression.

The univariate analysis of post-operative systemic complications as shown in table 5. We found no statistically significant association of interrupted antiplatelets to increase the post-operative systemic complications (OR 1.362, 95% CI 0.440-4.216, p = 0.592). However, ASA tended to have a higher risk of post-operative systemic complications without statistical significance (OR 3.583, 95% CI 0.462-27.820, p = 0.222) than clopidogrel (OR 1.865, 95% CI 0.233-14.934, p = 0.557). Additionally, there were some variables that found no associations with increased post-operative systemic complications included IAT, ASA, clopidogrel, type 2 diabetes mellitus, hypertension, coronary artery disease, heart valve disease, and hyperlipidemia.

Table 5. Univariate Analysis for Post-operative Systemic Complications.

Risk Factors	Systemic Complication (n = 13)	No Systemic Complication (n = 561)	OR† (95% CI)	p-value
Interrupted antithrombotic drug - no.(%)	8 (61.54)	260 (54.01)	1.362 (0.440-4.216)	0.592
Aspirin	7 (58.33)			
Clopidogrel	1 (7.69)			
Antithrombotic regimens – no. (%)				
Aspirin	12 (92.31)	432 (77.01)	3.583 (0.462-27.820)	0.222
Clopidogrel	1 (7.69)	24 (4.28)	1.865 (0.233-14.934)	0.557
Warfarin	0	71 (12.66)	N/A	N/A
Aspirin + Clopidogrel	0	25 (4.46)	N/A	N/A
Aspirin + Warfarin	0	9 (1.60)	N/A	N/A
Dental procedures – no. (%)				
Tooth extraction	13 (100.00)	519 (92.51)	N/A	N/A
Surgical removal	0	2 (0.36)	N/A	N/A
Torectomy	0	43 (7.68)	N/A	N/A
Male sex – no. (%)	9 (69.23)	302 (53.83)	0.518 (0.158-1.703)	0.279
Age – year (mean ± SD)	64.46 ± 9.947	66.94 ± 10.65	0.980 (0.933-1.028)	0.403
Medical history – no. (%)				
Type 2 diabetic mellitus	8 (61.54)	271 (48.31)	1.712 (0.553-5.298)	0.351
Hypertension	9 (69.23)	383 (68.27)	1.046 (0.318-3.441)	0.941
Coronary artery disease	3 (23.08)	120 (21.39)	1.102 (0.299-4.069)	0.884
Stroke	1 (7.69)	116 (20.68)	0.320 (0.041-2.484)	0.276
Atrial fibrillation	0	45 (8.02)	N/A	N/A
Heart valve disease	1 (7.69)	17 (3.03)	2.667 (0.328-21.697)	0.359
Hyperlipidemia	6 (46.15)	211 (37.61)	1.422 (0.472-4.287)	0.532
Chronic kidney disease	0	41 (7.31)	N/A	N/A
Neurologic disease	1 (7.69)	108 (19.25)	0.350 (0.045-2.717)	0.315

OR: odds ratio; no.: number of patients; SD: standard deviation; N/A: not available; †simple logistic regression.

Discussion

Our analyses demonstrated that the relationship of CAT and post-operative bleeding was not statistically significant (adjusted OR 0.446, 95% CI 0.080-2.494, p = 0.358). This finding supported by Yang Set al. 2016 (28) conducted a meta-analysis included 6 randomized controlled studies or controlled clinical studies in 591 patients taking oral anticoagulants and underwent dental extractions. The results revealed that patients who continued oral anticoagulants had a non-significant risk of post-operative bleedings compared with patients who discontinued oral anticoagulant therapy (risk ratio 1.31, 95% CI 0.79–2.14).

Interesitngly, we found that warfarin was a strong risk factor for post-operative bleedings ($p < 0.001$). In contrast, ASA was less likely to cause bleedings post-operatively (p = 0.005). Our results supported by Lu et al., 2018 reported that continuation of warfarin had a strong trend of higher incidence of bleeding after dental extraction than a continuation of single or dual and antiplatelet regimens (9.1% and 1.82%, respectively, p = 0.0599) (29). Results from Bajkin et al., 2014 showed that patients who continued dual antiplatelet regimen had a 1.7% incidence of bleeding after dental extraction, and no bleeding was reported in continuation of single antiplatelet treatment (30). Furthermore, we were the first to report the association of atrial fibrillation as a statistically significant comorbid condition to increase post-operative bleedings after oral minor surgery (OR 9.375, 95% CI 2.031–43.277, p = 0.004). However, the data showed with a low precision due to the wide range of 95% confidence intervals and should be determined in a larger study.

This study showed trends of INR in the therapeutic levels towards post-operative bleedings without statistical significance. These results are supported by previous studies, Phanpaisan et al., 2015 They demonstrated that the incidences of post-operative bleeding were comparable between patients with INR in therapeutic and supratherapeutic levels (4.88% and 3.66%, respectively) (31). Morimoto et al., 2008 showed that patients with target INR levels had a higher incidence of bleedings than patients with out-of-target INR levels (10.09% and 2.50% respectively) and reported the INR was not correlated to post-operative bleedings (p = 0.06) (12).

Our analyses demonstrated that an interruption of antithrombotic drugs had a trend towards post-operative systemic complications without statistical significance (adjusted OR 1.422, 95% CI 0.454–4.452, p = 0.545). Although the total incidence of systemic complications was low as 2.26% and all the events occurred in patients who taking antiplatelets. We found that ASA had a trend without statistical significance (OR 3.583, 95% CI 0.462-27.820, p = 0.222) to increase systemic complications than clopidogrel (OR 1.865, 95% CI 0.233-14.934, p = 0.557). Maulaz et al., 2005 reported from patients in a stroke unit that the interruption of ASA at least 3 days was associated with an increased risk of ischemic stroke or transient ischemic attack (OR 3.40, 95% CI 1.08–10.63) (32). There are several previous studies reported that discontinuing the antiplatelet drugs can increase the risk of thromboembolic events particularly myocardial infarction, stent thrombosis, and stroke. (33-39) Therefore, overestimation of severe post-operative bleeding risk from dental extraction which

considered as low potential, may increase the risk of thromboembolic event and potentially harm to develop consequences of morbid complications.

Interestingly, there was no systemic complication reported in patients who interrupted warfarin in our study, which might due to longer half-life of warfarin compared to antiplatelets. (13–21) However, the systemic complications that occurred in duration of longer than 30 days after procedure were likely to be confounded from other unmeasured factors than the interruption of antiplatelets for minor oral surgery.

Limitations

The mean age of patients in this study was relatively old, which may not reflect the younger population. As an observational retrospective study, potential confounding factors that were unable to control or measure may exist, leading to underestimate or overestimate the outcomes particularly other clinical factors related to bleedings or systemic complications. Moreover, the quality and variety of data in medical charts or missing data could impact the analyses. In addition, an influent factor that was unable to measure is patient adherence to interrupt or continue the antithrombotic drugs as recommended by physicians or dentists, as well as the adherence to re-initiate the antithrombotic therapy. This study included torectomy, a higher risk of bleeding than tooth extraction, but our result showed no association with post-operative bleeding that might due to low incidence. Because the antithrombotic drugs in this study are limited to ASA, clopidogrel, and warfarin, the results could not be extrapolated to newer agents such as ticagrelor, prasugrel, or direct oral anticoagulants (DOAC). Finally, the limited number of patients and low incidences of post-operative complications might affect the precision of statistical results, which should be examined in a prospective and larger study.

Conclusions

Our findings demonstrated that the incidence of postoperative bleeding is low and not related to continuation of antithrombotic drugs, and more frequent in patients taking warfarin. Interruption of antithrombotic drugs was not related to the occurence of systemic complications. Although, the low incidence of systemic complications was reported, the result showed a slight trend without statistical significance of antiplatelet interruption towards systemic complications that should be determined in the future study. Continuing education should be encouraged to carefully evaluate an individual patient for bleeding and thrombosis risks before considering of interruption the antithrombotic therapy.

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References

1. Potocki M, Amenabar JM. Dental management of patients receiving anticoagulation or antiplatelet treatment. J Oral Sci. 2007;49(4): 253-8.

2. Phanpaisan N. Dental guideline for tooth extraction in patients who receive antithrombotic drugs [Internet]. Dental department of Siriraj Hospital. 2017 [cited 2019July 12]. Available from: https://www2.si.mahidol.ac.th/km/cop/clinical/dental/4962/.

3. Dogne JM, de Leval X, Benoit P, Delarge J, Masereel B, David JL. Recent advances in antiplatelet agents. Curr Med Chem. 2002;9(5): 577-89.

4. Chiang-ngernthanyakun K. Dental treatment planning for patients with bleeding tendency. SWU Dent J. 2018;11(1):98-120.

5. Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62(7):1187-9.

6. American Heart Association. Heart Disease and Stroke Statistics 2005 Update. Dallas, Texas: American Heart Association, 2005.

7. Napenas JJ, Hong CH, Brennan MT, Furney SL, Fox PC, Lockhart PB. The frequency of bleeding complications after invasive dental treatment in patients receiving single and dual antiplatelet therapy. J Am Dent Assoc. 2009;140(6):690-5.

8. Lillis T, Ziakas A, Koskinas K, Tsirlis A, Giannoglou G. Safety of dental extractions during uninterrupted single or dual antiplatelet treatment. Am J Cardiol. 2011;108(7):964-7.

9. Evans IL, Sayers MS, Gibbons AJ, Price G, Snooks H, Sugar AW. Can warfarin be continued during dental extraction? Results of a randomized controlled trial. Br J Oral Maxillofac Surg. 2002;40(3):248-52.

10. Bajkin BV, Popovic SL, Selakovic SD. Randomized, prospective trial comparing bridging therapy using low-molecular-weight heparin with maintenance of oral anticoagulation during extraction of teeth. J Oral Maxillofac Surg. 2009; 67(5):990-5.

11. Cannon PD, Dharma VT. Minor oral surgical procedures in patients on oral anticoagulants--a controlled study. Aust Dent J. 2003;48(2):115-8.

12. Morimoto Y, Niwa H, Minematsu K. Hemostatic management of tooth extractions in patients on oral antithrombotic therapy. J Oral Maxillofac Surg. 2008;66(1):51-7.

13. Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med. 1998;158(15):1610-6.

14. Wahl MJ. Myths of dental surgery in patients receiving anticoagulant therapy. J Am Dent Assoc. 2000;131(1):77-81.

15. Wahl MJ, Pinto A, Kilham J, Lalla RV. Dental surgery in anticoagulated patients--stop the interruption. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(2):136-57.

16. Wahl MJ. Dental surgery and antiplatelet agents: bleed or die. Am J Med. 2014;127(4):260-7.

17. Nematullah A, Alabousi A, Blanas N, Douketis JD, Sutherland SE. Dental surgery for patients on anticoagulant therapy with warfarin: a systematic review and meta-analysis. J Can Dent Assoc. 2009;75(1):41.

18. Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 2002;94(1):57-64.

19. Park MW, Her SH, Kwon JB, Lee JB, Choi MS, Cho JS, et al. Safety of dental extractions in coronary drug-eluting stenting patients without stopping multiple antiplatelet agents. Clin Cardiol. 2012;35(4):225-30.

20. Lu SY, Tsai CY, Lu SN, Lin LH. Is alternation of warfarin regimen necessary before dental extractions in Taiwanese patients? Results of a retrospective cohort study. J Dent Sci 2015; 10(4):352-8.

21. Lu SY, Tsai CY, Lin LH, Lu SN. Dental extraction without stopping single or dual antiplatelet therapy: results of a retrospective cohort study. Int J Oral Maxillofac Surg. 2016; 45(10):1293-8.

22. Task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33(20):2569-619.

23. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267–315.

24. van Diermen DE, van der Waal I, Hoogstraten J. Management recommendations for invasive dental treatment in patients using oral antithrombotic medication, including novel oral anticoagulants. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(6):709-16.

25. Szalma J, Joób-Fancsaly A, Dental management of hemorrhage-prone patients. Fogorv Sz. 2015;108(2):57-60.

26. Hicks KA, Stockbridge NL, argum SL, Temple RJ. Bleeding academic Research consortium consensus report: the food and drug administration perspective. Circulation. 2011;123(23):2664-5.

27. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23):2736-47.

28. Yang S, Shi Q, Liu J, Li J, Xu J. Should oral anticoagulant therapy be continued during dental extraction? A meta-analysis. BMC Oral Health. 2016;16(1):81.

29. Lu SY, Lin LH, Hsue SS. Management of dental extractions in patients on warfarin and antiplatelet therapy. J Formos Med Assoc. 2018;117(11):979-86.

30. Bajkin BV, Urosevic IM, Stankov KM, Petrovic BB, Bajkin IA. Dental extractions and risk of bleeding in patients taking single and dual antiplatelet treatment. Br J Oral Maxillofac Surg. 2015;53(1):39-43.

31. Phanpaisan N, Chokchaivorrakul W. Incidence of Postoperative Bleeding After Dental Extraction in Patients Receiving Antithrombotic Drugs. J Mahidol R2R e-journal. 2015;2(2):25-35.

32. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Intern Med. 2005;62(8):1217-20.

33. Bosch X, Marrugat J, Sanchis J. Platelet glycoprotein IIb/IIIa blockers during percutaneous coronary intervention and as the initial medical treatment of non-ST segment elevation acute coronary syndromes. Cochrane Database Syst Rev. 2013;(10):CD002130. doi: 10.1002/14651858.CD002130.pub3.

34. Kitchen L, Erichson RB, Sideropoulos H. Effect of drug-induced platelet dysfunction on surgical bleeding. Am J Surg. 1982;143(2):215-7.

35. Biondi-Zoccai GGL, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J. 2006;27(22):2667-74.

36. Grines CL, Bonow RO, Casey Jr DE, Gardner TJ, Lockhart PB, Moliterno DJ, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation. 2007;115(6):813-8.

37. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation. 2006;113(24):2803-9.

38. Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneousoperation. J Am Acad Dermatol. 2003; 48(2):233-7.

39. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromesfollowing aspirin withdrawal: a special risk for late stent thrombosis. J AmColl Cardiol. 2005;45(3):456-9.

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