

Risk of Bleeding in Patients on Antiplatelet Therapy undergoing Minor Oral Surgical Procedures: A Systematic Review and Meta-analysis

Sanjay Joshi¹, Bhupendra Mhatre², Avadhut T Phad³, Arsalan Ansari⁴

ABSTRACT

Background: Planning dental extractions for patients on antiplatelet therapy remains a controversy. The decision to stop the antiplatelet therapy before dental extraction because of the risk of bleeding remains questionable.

Aim/objective: We conducted a meta-analysis to assess the risk of oral bleeding complications after dental procedures in patients on antiplatelet therapy.

Search methods: PubMed, Science Direct, and Google scholar databases were screened from January 1, 1949, to January 1, 2019, for eligible articles. Studies involving single and dual antiplatelet therapy patients undergoing invasive dental procedures that induce oral bleeding were searched, and a meta-analysis was conducted.

Result: This meta-analysis included four studies, the quantitative results indicated that the risk of postoperative bleeding with continuing antiplatelet therapy is (risk difference = 0.0154, 95% confidence interval [-0.00619 to 0.0369]; $p = 0.162$) the heterogeneity ($I^2 = 0.00\%$, $p = 0.162$). There was no statistically significant difference between the postoperative bleeding rate ($p = 0.162$).

Conclusion: This meta-analysis suggests no need to modify or discontinue antiplatelet therapy before performing minor oral surgical procedures.

Keywords: Antiplatelet therapy, Dental extraction, Hemorrhage, Minor oral surgical procedures, Risk of bleeding.

Key message: The risk of postoperative bleeding was increased with antiplatelet therapy, but local hemostatic methods might control it. The result of this meta-analysis supports performing minor oral surgical procedures while continuing the antiplatelet therapy.

Journal of Contemporary Dentistry (2021): 10.5005/jp-journals-10031-1306

INTRODUCTION

Antithrombotic drugs were classified as the drug that affects platelet aggregation and clot formation.¹

In most cases of the acute coronary syndrome, the most frequently used antiplatelet drug combination was aspirin with clopidogrel. The other drug combination, which was not commonly used, is dipyridamole with aspirin in a stroke patient because clopidogrel alone was more effective and well-tolerated by patients. The currently licensed newer antiplatelet drugs prescribed for patients with acute coronary syndrome are prasugrel and ticagrelor. These are the only drugs that can be prescribed together with aspirin. The current evidence using prasugrel and ticagrelor in context to the risk of bleeding during minor surgical procedures is minimal.² Aspirin in a combination of clopidogrel used as a dual antiplatelet therapy to prevent the thrombotic event. Despite so much benefit of antiplatelet agents, it cannot be ignored that these drugs could increase the risk of intraoperative or postoperative bleeding.³

The purpose of this systematic review and meta-analysis was to study and review the current and existing literature on oral bleeding complications in minor oral surgical procedures in patients who are on antiplatelet therapy.

MATERIALS AND METHODS

Protocol and Registration

This systematic review is performed as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines

¹⁻⁴Department of Oral and Maxillofacial Surgery Terna Dental College, Navi Mumbai, Maharashtra, India

Corresponding Author: Avadhut T Phad, Department of Oral and Maxillofacial Surgery, Terna Dental College and Hospital, Navi Mumbai, Maharashtra, India, Phone: +91 07977004128, e-mail: avdhut.phad@gmail.com

How to cite this article: Joshi S, Mhatre B, Phad AT, *et al.* Risk of Bleeding in Patients on Antiplatelet Therapy undergoing Minor Oral Surgical Procedures: A Systematic Review and Meta-analysis. *J Contemp Dent Pract* 2021;x(x):xx-xx.

Source of support: Nil

Conflict of interest: None

(PRISMA), which was aimed to assess the risk of a bleeding complication in people on oral antiplatelet therapy undergoing a minor oral surgical procedure.

Focused Question

Is there any risk of a bleeding complication in people on oral antiplatelet therapy undergoing a minor oral surgical procedure?

Objectives

We aimed to assess the risk of bleeding complications in people on oral antiplatelet therapy undergoing minor oral surgery.

Eligibility Criteria

Inclusion Criteria

- Randomized controlled trials (RCTs), cohort, controlled clinical trials (CCTs).
- All articles were published in the English language.
- Studies in which patients on at least one antiplatelet drug undergoing minor oral surgery with or without discontinuing the antiplatelet therapy.
- Studies with measurements of bleeding outcomes during and after minor oral surgical procedures.
- Studies between January 1, 1949, and January 1, 2019, were included.

Exclusion Criteria

- Studies in which patients on vitamin K antagonists, heparin, and newer anticoagulant drugs.
- Any hemocoagulopathy was excluded.
- Studies with a lack of data could not be used for our systematic review.
- Laboratory studies, animal studies, case reports, letters to the editor, reviews, guidelines, and expert opinions.

PICO

P—Participants—people of all ages who are on at least one antiplatelet drug without any blood dyscrasias.

I—Intervention—minor oral surgical procedures.

C—Comparison—patients who never took any antiplatelet therapy or those who were on antiplatelet drugs but discontinued the same before performing minor surgical procedures.

O—Outcome—number of participants with intraoperative and postoperative bleeding episodes.

Information Sources

We performed the literature search that fulfills this study's inclusion and exclusion criteria, including published and unpublished trials with restrictions on the English language, year, and publication status.

Electronic Searches

We searched Science direct, PubMed, and Google scholar databases and trial registries.

Manual Search

We reviewed the references of included studies and various systematic reviews to check any references that could meet the study's inclusion criteria. We also performed a manual search using Terna dental college library resources.

Search Strategy

Keywords

Antiplatelet therapy	Acetylsalicylic acid (ASA), Clopidogrel, Ticlopidine, Triflusal, dual antiplatelet therapy, single antiplatelet therapy.
Minor oral surgical procedures	Extraction of teeth, maxillofacial surgeries.
Risk of bleeding	Intraoperative bleeding, Postoperative bleeding.

We searched the different databases with the time frame between 1949 and 2019. Literature searching was started under the subject heading of ((minor oral surgery) AND antiplatelet therapy) AND risk of bleeding, ((minor oral surgical procedures) AND antiplatelet therapy) AND bleeding risk, (((antiplatelet therapy) AND dental extraction) OR minor oral surgery) AND bleeding risk, ((antiplatelet therapy) AND extraction) OR minor oral surgical procedure AND risk of bleeding.

Study Selection

Studies included patients undergoing minor oral surgical procedures and antiplatelet therapy, which induces oral bleeding. The included articles were published in the English language only.

Data Extraction and Management

The data extraction was performed from included studies and with the help of data extraction form, which included study participants' characteristics and all outcome measures. We collected the data according to the Cochrane checklist and tabulated the form using per general template.

Data Collection Process

For data collection, we used the MS excel sheet (version 2013), and initially, data were collected from one article, reviewed by senior faculty, and finalized. Moreover, the same pattern of data extraction was followed for the remaining articles.

Assessment of Risk of Bias in Included Studies

We assessed the risk of bias for each selected article using RevMan (Review manager 5.3) software and categorized it into high risk, low risk, and unclear. Furthermore, it created a "risk of bias" plot (Figs. 1 and 2).

Three RCT were classified under low risk of random sequence generation bias, and the remaining one was high. The total number of the included studies is four, in which one was categorized as low risk, two were in the high-risk category, and one study was not clear about the blindness of participants.

Footnotes

*Green: Low-risk bias

*Blank: Unclear risk of bias

*Red: High-risk Bias

Data Synthesis

We assumed that included trials use different outcome definitions of postoperative bleeding. We used the number of episodes of bleedings postoperatively as a parameter. We choose this parameter as a primary parameter because various literature used different measurements to record postoperative bleeding.

Data Items

- Study ID—ID of the included study.
- Author—author and publication year.
- Participants—people of all ages on continuous antiplatelet therapy and no other blood diseases.
- Interventions—patients on oral antiplatelet therapy undergoing minor oral surgical procedures.
- Comparison—patients who never took any antiplatelet therapy or those who were on antiplatelet therapy and discontinued the same before undergoing the minor oral surgical procedure.
- Outcomes—number of participants with postoperative bleeding episodes.

	Randomisation	Allocation concealment?	Blinding of participants	Blinding of assessment	Incomplete outcome data	Selective reporting
Alexander grobe 2015	+	+	+	+	-	+
Ardekian et al 2000		+	-	-	+	+
Cardona tortajada 2009	+		-		+	+
Mahan-won park 2012	+	+				-

Fig. 1: Risk of bias plot

- Study design—whether randomized or nonrandomized clinical trials.
- Main findings—the number of patients in whom bleeding was reported.

Study Selection

See the [Flowchart 1](#) and [Table 1](#).

Statistical Analysis

All statistical analyses were performed using Medcalc statistical software version 18.1.1 (MedCalc Software bvba, Ostend, Belgium). Assessment of meta-analysis was done using the standard mean difference and risk difference with a 95% confidence interval. For assessment of heterogeneity, we used I^2 statistic, with the score of 25 (low), 50 (medium), and 75 (high). We used the random model due to literature and created a funnel map to determine publication bias.

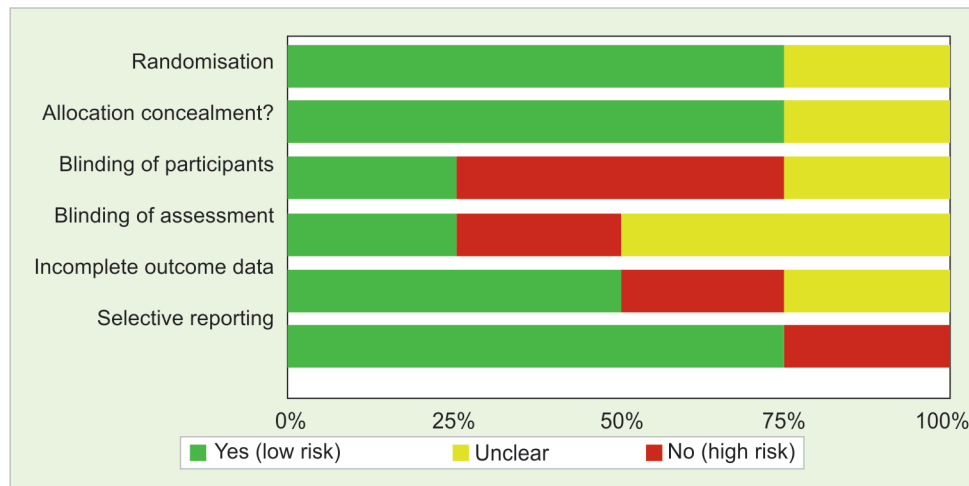


Fig. 2: Risk of bias plot

Flowchart 1: Prisma flow diagram

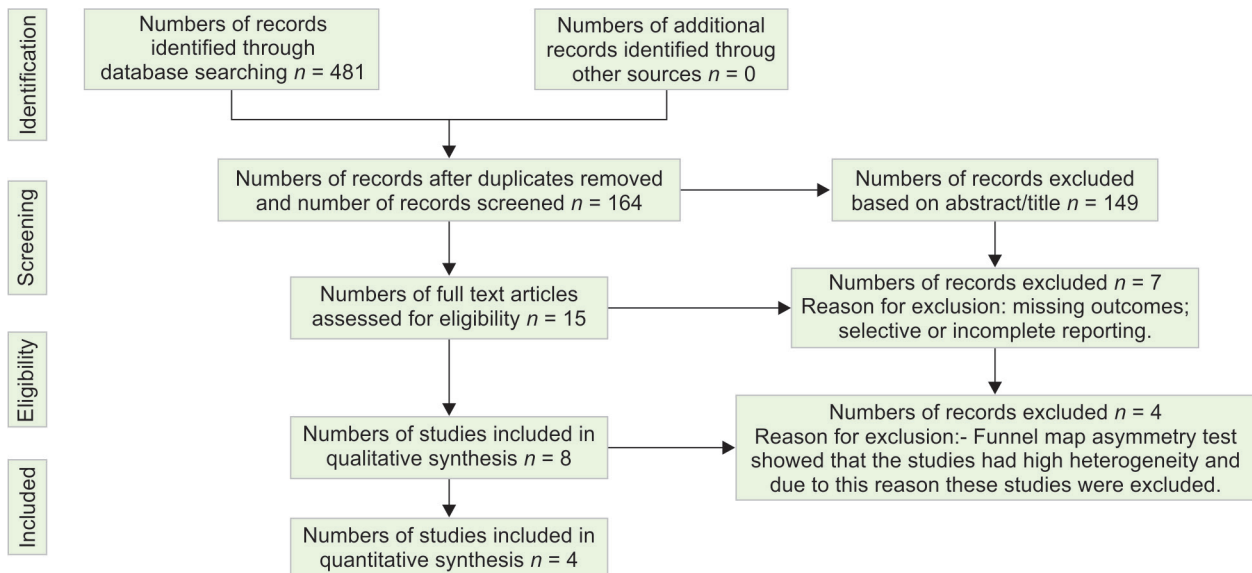


Table 1: Study

Sl. No.	Study	Study and type	Dental procedures	Total no. of patient	Control/placebo group(s)	Intervention group(s)	Study parameter	Main findings
1	Ardekian et al. ⁴	Cohort	Extractions (single and multiple)	39	Stopped ASA therapy 7 days before (<i>n</i> = 20)	Daily ASA therapy (75–150 mg) (<i>n</i> = 19)	Intraoperative bleeding (Blood loss of less than 20 mL was considered mild; between 20 and 50 mL, moderate; and more than 50 mL, severe.)	Out of 20 control group patients, 2 encountered post-operative bleeding and out of 19 study group patients, 4 of them encountered postoperative bleeding.
2	Cardona-Tortajadan et al. ⁵	Cohort	Extractions (single and multiple)	155	None (though 22 patients reported interruption of therapy before extraction)	ASA therapy (100–300 mg; <i>n</i> = 118) Clopidogrel (75 mg; <i>n</i> = 20) Ticlopidine (250 mg; <i>n</i> = 2) Triflusal (<i>n</i> = 15)	Postoperative bleeding (monitoring after 10 minutes; monitoring by phone 24 hours later with three possibilities: a) No problems b) Still bleeding c) Bleeding did occur and had been controlled.	Out of 22 control group patients, 3 encountered post-operative bleeding and out of 134 study group patients, 23 of them encountered postoperative bleeding.
3	Park et al. ⁶	Cohort	Extractions (single and multiple)	200	Patients never having received any antiplatelet therapy, matched control subjects (<i>n</i> = 100)	Daily ASA (100–200 mg) and clopidogrel (75 mg; <i>n</i> = 59) Daily ASA (100–200 mg), clopidogrel (75 mg) and cilostazol (100 mg; <i>n</i> = 41)	Intraoperative and Postoperative bleeding (1) Excessive intra-extraction blood loss, (2) Transfusion, (3) Re-hospitalization for bleeding. Less than 30 mL blood loss was considered not excessive, and more than 30 mL was considered excessive.	Out of 100 control group patients, 1 encountered post-operative bleeding and out of 100 study group patients, 2 of them encountered postoperative bleeding.
4	Gröbe et al. ⁷	Cohort	Oral osteotomy	405	Not under any anticoagulation or antiplatelet (<i>n</i> = 281)	Mono antiplatelet (<i>n</i> = 64) and dual antiplatelet (<i>n</i> = 60)	Postoperative bleeding (an event that required additional surgical intervention.)	Out of 281 control group patients, 2 encountered post-operative bleeding and out of 124 study group patients, 3 of them encountered postoperative bleeding.

In the search process, duplicates were removed and 15 studies were included after a thorough search of PubMed, Science Direct, and Google scholar databases. Out of 15 studies, seven studies were expelled due to missing outcomes, selective or incomplete reporting.^{8–10,12,13,16,18} And remaining eight CCTs were included in the meta-analysis. The study details and quality assessment of included studies are shown in Table 2.

This meta-analysis included the total number of 4,575 patients divided into intervention groups in which patients on prolong antiplatelet therapy (1,468) and the control group included 3,107 patients who did not take any antiplatelet treatment and those who discontinued antiplatelet therapy 3 to 5 days before undergoing the minor oral surgical procedure.

Test for Heterogeneity

<i>Q</i>	58.5684
<i>DF</i>	7
Significance level	<i>p</i> < 0.0001
<i>I</i> ² (inconsistency)	88.05%
95% CI for <i>I</i> ²	78.72–93.29

Risk Difference Evaluation (without Excluding Publication Bias)

This meta-analysis was performed based on primary parameters, i.e., episodes of postoperative bleeding. In the intervention group,

Table 2: Meta-analysis: risk difference—bleeding

Study	Intervention	Controls	Risk difference	95% CI	Z	p	Weight (%)	
							Fixed	Random
Ardekian et al. ⁴	4/19	2/20	0.111	−0.115 to 0.336			0.13	1.64
Cardona-Tortajadan et al. ⁵	23/134	3/22	0.0353	−0.122 to 0.192			0.27	3.11
Lillis et al. ¹¹	24/111	2/532	0.212	0.136 to 0.289			1.11	8.59
Park et al. ⁶	2/100	1/100	0.0100	−0.0237 to 0.0437			5.77	15.55
Girotra et al. ¹⁷	18/546	15/575	0.00688	−0.0130 to 0.0267			16.60	17.79
Gröbe et al. ⁷	3/124	2/281	0.0171	−0.0117 to 0.0459			7.90	16.40
Bajkin et al. ¹⁴	1/160	0/105	0.00625	−0.00596 to 0.0185			43.87	18.68
Lu et al. ¹⁵	5/274	10/1472	0.0115	−0.00494 to 0.0278			24.34	18.23
Total (fixed effects)	80/1468	35/3107	0.0339	0.0208 to 0.0470	5.084	<0.001	100.00	100.00
Total (random effects)	80/1468	35/3107	0.0300	−0.000228 to 0.0602	1.945	0.052	100.00	100.00

Table 3: Meta-analysis: risk difference—bleeding (excluding publication bias)

Variable for studies		Study	
1. Intervention groups			
Variable for total number of cases		Study_N	
Variable for number of positive cases		Bleeding_S	
2. Control groups			
Variable for total number of cases		Control_N	
Variable for number of positive cases		Bleeding_C	

Study	Intervention	Controls	Risk difference	95% CI	Z	p	Weight (%)	
							Fixed	Random
Ardekian et al. ⁴	4/19	2/20	0.111	−0.115 to 0.336			0.91	0.91
Cardona-Tortajadan et al. ⁵	23/134	3/22	0.0353	−0.122 to 0.192			1.89	1.89
Park et al. ⁶	2/100	1/100	0.0100	−0.0237 to 0.0437			41.04	41.04
Gröbe et al. ⁷	3/124	2/281	0.0171	−0.0117 to 0.0459			56.16	56.16
Total (fixed effects)	32/377	8/423	0.0225	−0.00632 to 0.0514	1.531	0.126	100.00	100.00
Total (random effects)	32/377	8/423	0.0154	−0.00619 to 0.0369	1.397	0.162	100.00	100.00

of 1,468 patients 80 show postoperative bleeding, and in the control group, of 3,107 patients 35 show postoperative bleeding.

A significant increase in postoperative bleeding was seen in the intervention group [RD = 0.0300, 95% CI (−0.000228 to 0.0602); $p = 0.052$] (Table 2). The random model, funnel map, and forest plot (Figs 3 and 4) showed that studies of Lillis et al.,¹¹ Bajkin et al.,¹⁴ Lu et al.,¹⁵ Girotra et al.¹⁷ had high heterogeneity ($I^2 = 88.05\%$ $p = 0.052$), and due to this reason, these studies were excluded. In the included studies, the rate of postoperative bleeding did show significant bias in the sensitivity analysis.

After excluding the four biased studies, the definitive studies with their details and the quality analysis results are shown above in Table 3.

Test for Heterogeneity

Q	1.2819
DF	3
Significance level	$p = 0.7334$
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00–69.79

The incidence of postoperative hemorrhage was 32 out of 377 in the continuing antiplatelet therapy group (intervention group) and 8 out of 423 in the stopping antiplatelet therapy group (control group). A significant increase in postoperative bleeding was seen in the intervention group [RD = 0.0154; 95% CI (−0.00619 to 0.0369); $p = 0.162$] (Table 3). In the heterogeneity ($I^2 = 0.00\%$ $p = 0.162$), the random model was used. The funnel map and forest plot (Figs 5 and 6) showed that the studies of Ardekian et al.,⁴ Cardona-Tortajadan et al.,¹⁹ Park et al.,⁶ and A Gröbe et al.⁷ are symmetrical and the bias in the sensitivity analysis did not show a significant risk of postoperative bleeding.

DISCUSSION

Antithrombotic drugs were broadly classified into two types—the drugs that affect the function of platelet aggregation and secondly those that prevent clot formation. The drugs that affect platelet aggregation are antiplatelet drugs. Platelet aggregation was activated by several endogenous mediators that include prostaglandin thromboxane, adenosine diphosphate (ADP), thrombin, and fibrin. Antiplatelet drugs include aspirin and other nonsteroidal anti-inflammatory drugs that inhibit thromboxane

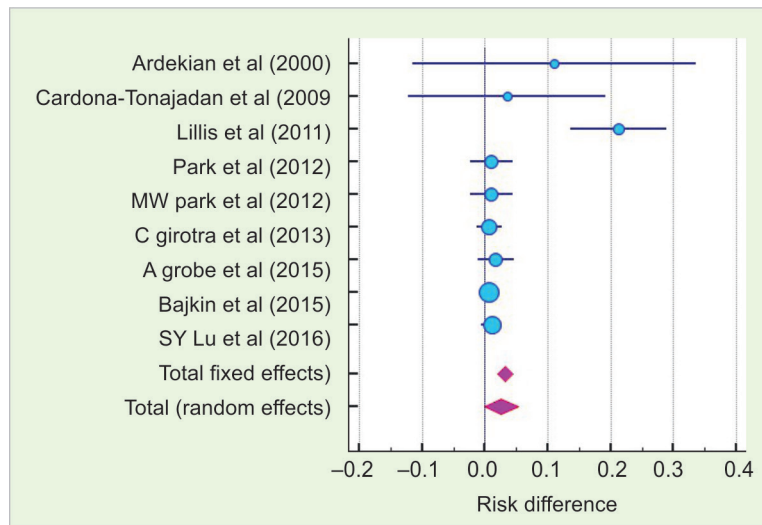


Fig. 3: Forest plot: risk difference (bleeding)

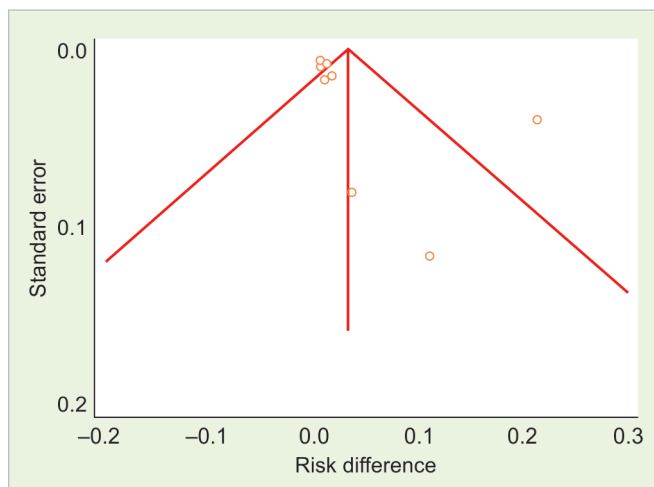


Fig. 4: Funnel plot: risk difference (bleeding)

synthesis by blocking the enzyme cyclooxygenase whereas abciximab and tirofiban are glycoproteins IIb/IIIa receptor inhibitors, and antagonists of ADP receptors are clopidogrel and ticlopidine.¹ According to the American Heart Association guideline, dual antiplatelet therapy can be used for secondary prevention of acute coronary syndrome.²⁰ But with dual antiplatelet therapy, there will be an increase in the risk of postoperative bleeding.²¹

The study by Hirsh et al. has shown that with the use of aspirin with clopidogrel as dual antiplatelet therapy, there was an increase in post-extraction bleeding by 0.4 to 1.0%.²¹ According to the study by Balasubramanian et al.,⁸ there is no need to stop or alter the antiplatelet medication for routine dental extractions because there was no significant increased postoperative bleeding in the patient on antiplatelet therapy.⁸ Stopping antiplatelet drugs 3 to 5 days before the minor oral surgical procedure has become common in the general clinical practice.

As per Canadian cardiovascular guidelines, patients on aspirin therapy can be taken for minor oral surgical procedures. In dual antiplatelet therapy, the patients should discontinue the medication 7 to 10 days prior to the surgery.²²

From this meta-analysis of four studies, it can be concluded that antiplatelet drugs could be continued while performing minor oral surgical procedures, and if bleeding occurs, it can be controlled by local hemostatic measures. The studies performed by Lillis et al.,¹¹ Girotra et al.,¹⁷ Bajkin et al.,¹⁴ and Lu et al.¹⁵ had more significant heterogeneity. Patients who continued antiplatelet therapy had increased postoperative bleeding than those who stopped antiplatelet therapy before undergoing minor oral surgical procedures, but local hemostatic measures could manage it. Postoperatively the patient who continued antiplatelet therapy should be managed by simple hemostatic methods, such as pressure pack and suturing before being discharged. A thorough history should be taken especially systemic diseases and current medication, which may interfere with normal bleeding and clotting time.² There is other evidence in the research that shows patients could effectively avoid the risk of postoperative bleeding without stopping antiplatelet therapy by limiting the number of teeth removed, preoperative evaluation, atraumatic surgical procedure, and correct postoperative management.²³ One of the causes of aspirin withdrawal syndrome was blind discontinuation of antiplatelet drugs, which may lead to life-threatening thromboembolic events, such as myocardial infarction and stroke,²⁴ so it is more beneficial to continue than the withdrawal of these drugs.

LIMITATIONS

Only the RCT, non-RCT, and cohort studies were included in the systematic review and meta-analysis. Other studies, such as case studies, case reports, case series, and *in-vitro* studies, were not included in this review. This review included studies from January 1, 1949, to January 1, 2019. Hence, the studies published post January 1, 2019, were excluded from the review, and this may prevent determining the current trends in the postoperative risk of bleeding in the year 2019.

CONCLUSION

This meta-analysis supports that minor oral surgical procedures can be performed without discontinuing antiplatelet drugs. Some factors like poor periodontal conditions and periapical

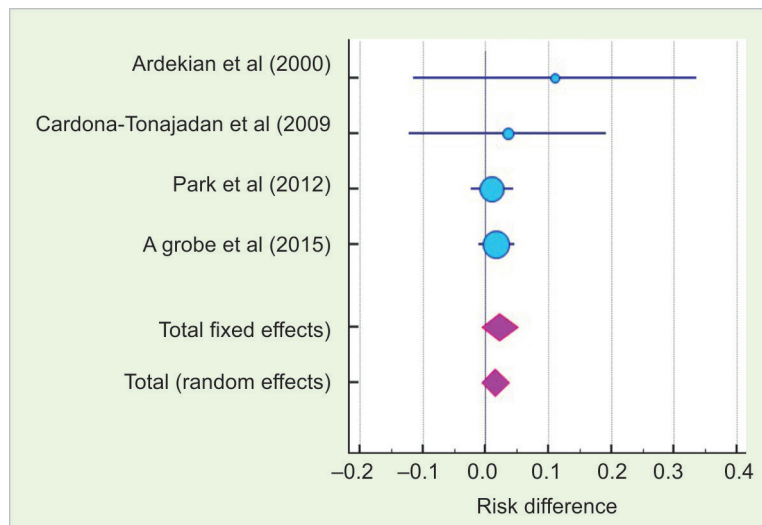


Fig. 5: Forest plot: risk difference—bleeding (excluding publication bias)

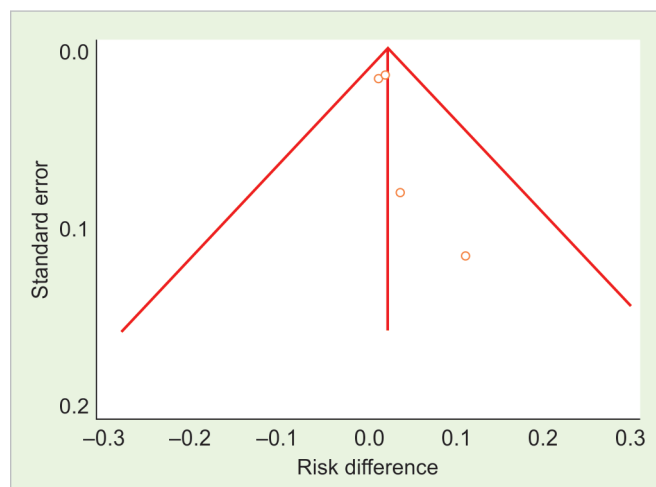


Fig. 6: Funnel plot: risk difference—bleeding (excluding publication bias)

pathologies cause an increase in postoperative bleeding and are managed by local hemostatic measures. More RCTs will be required to evaluate the effect of antiplatelet drugs on postoperative bleeding thoroughly. According to this meta-analysis, minor oral surgical procedures can be performed without modification or discontinuation of antiplatelet drugs.

FUTURE IMPLICATIONS

More RCTs comparing the postoperative bleeding risk with the continuation of antithrombotic agents should be performed with definite measurable parameters. Studies should also have strict inclusion and exclusion criteria that follow proper randomization protocol. The statistical analysis should be performed for the correct sample size, allowing statistically significant findings to minimize the risk of bias.

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