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Systematic Review and Meta-Analysis
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Postoperative bleeding risk of direct oral anticoagulants after oral surgery procedures: a systematic review and meta-analysis

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Abstract. Direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban; DOACs) have been introduced to improve safety and superior therapeutic value compared to their predecessors such as warfarin or enoxaparin. The aim of this systematic review and meta-analysis was to assess the postoperative bleeding risk of DOACs during oral surgery procedures. Systematic searches were performed in electronic databases including PubMed, Scopus, Web of Science and Cochrane Library. Thirteen studies were included in the qualitative synthesis: two retrospective case–control studies, five prospective case–control studies, three cross-sectional studies, two case series and a case report; while only six studies were statistically analysed. The risk ratio of postoperative bleeding in DOACs patients was significantly greater than in healthy patients (3.04; 95% confidence interval (CI) = 1.31–7.04). This is especially true for rivaroxaban (4.13; 95% CI = 1.25–13.69), and less so for dabigatran which presented a risk ratio similar to that of healthy patients (1.00; 95% CI = 0.21–4.82). However, further research is required to support these results. Both apixaban and edoxaban were excluded from statistical analysis due to the lack of clinical studies.

Keywords: direct oral anticoagulants; oral surgery; postoperative bleeding risk; meta-analysis.

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Warfarin and other coumarin derivatives have been the only available options for oral anticoagulation for over 60years. However, this kind of therapy has various limitations, such as the slow onset of action with the need for initial bridging with heparin[1], the multiple food and drug interactions, the common genetic polymorphisms that affect its metabolism and the narrow therapeutic index and need for monitoring[2,3]. Direct oral anticoagulants (DOACs), the so-called 'new oral anticoagulants', has been introduced for the last 20–30 years to improve adherence with anticoagulants therapy and to minimize discomforts connected with it;

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these can be administerd in fixed doses once or twice daily, are not affected by food and there are few drug–drug interactions. These drugs are now approved for the acute treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), for the prevention of stroke and systemic embolization in non-valvular atrial fibrillation (NVAF), for venous thromboembolism (VTE) prophylaxis after orthopaedic surgery and in hospitalized medically ill patients, and for the management of acute coronary syndrome (ACS)[4]. Various terms have been used to describe this class of anticoagulants such as novel/new oral anticoagulants (NOACs), direct oral anticoagulants (DOACs) and target-specific oral anticoagulants (TSOACs)[3,5]; the use of the former term could lead to confusion because in medicine 'No AC' denotes that the patient is not taking an anticoagulant[3]. The use of multiple terms and abbreviations can lead to fragmentation of the medical literature; for this reason the International Society on Thrombosis and Haemostasis Scientific and Standardisation Committee has adopted the term 'direct oral anticoagulants'[5]. Nowadays, DOACs available in commerce can be divided into two classes, namely direct factor Xa (FXa) inhibitors (Rivaroxaban, Apixaban and Edoxaban) and direct thrombin inhibitors (dabigatran etexilate). The first direct thrombin inhibitor that was found to be comparable with warfarin was Ximelagatran, but it has never been approved by the US Food and Drug Administration (FDA) due to its liver toxicity[1]. Since then, many other drugs have been tested such as Tanogitran, Eribaxaban, Fidebaxaban, Darexaban and Letaxaban. These are direct FXa inhibitors evaluated in phase II clinical trial studies; the development of Darexaban and Letaxaban was discontinued in 2011[6]. Instead, on 23 June 2017 another direct FXa inhibitor, Betrixaban, was approved by the FDA and will become available between August and November 2017[7]. Dabigatran etexilate is a potent, non-peptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule. Rivaroxaban, apixaban and edoxaban bind to the active site of FXa, either FXa in solution or FXa incorporated within the prothrombinase complex or associated with a clot, and inhibit the enzyme in a rapid, reversible and competitive fashion[8,9]. Dabigatran is excreted at 80% by the kidneys, while rivaroxaban has a 67% renal elimination and 33% faecal elimination, and apixaban is eliminated at 25% by the kidneys and 75% by the liver. DOACs' anticoagulation effects do not require routine laboratory monitoring[10]. Vitamin K antagonists (VKAs) act on a different point of the coagulation cascade; their mechanism of action is through antagonism of vitamin K-dependent synthesis of coagulation factors by binding to vitamin K reductase; coagulation factors that are decreased by VKA include thrombin, factors VII, IX and X, as well as proteins C and S[11]. VKAs have a hepatic elimination. The international normalized ratio (INR) allows the measurement and monitoring of the effect of VKA anticoagulation. Guidelines for the management of VKA patients during oral surgery procedures have been widely described: for an INR value between 2 and 4, the discontinuation of VKA is unnecessary without a significantly higher risk of postoperative bleeding[12]. Unlike VKAs and aspirin[13], universally accepted consensus on the perioperative management of DOACs patients during oral surgery procedures is not available, although many authors have expresses their personal approaches to DOACs[14–20]. The aim of the present meta-analysis is to review the available literature on DOACs patients during oral surgery and to define the postoperative bleeding risk after these kinds of procedures, and to compare them with VKAs patients.

Materials and methods

A systematic review protocol was performed according to the PRISMA (Preferred Reporting Items Systematic review and Meta-Analyses) Statement[21].

Focused question

The focus questions were: (1) is the DOACs therapy associated with an increased postoperative bleeding rate after oral surgery? (2) Do dabigatran, rivaroxaban, apixaban and edoxaban have different postoperative bleeding risks? (3) Is there a difference in terms of postoperative bleeding between DOACs and VKAs?

Eligibility criteria

All observational studies investigating the risk of postoperative bleeding in patients under DOAC therapy after any kinds of oral surgery procedures were considered eligible.

The inclusion criteria were: (1) study design – all kinds of studies describing postoperative risk of DOACs patients after oral surgery procedures; (2) studies written in English. The exclusion criteria were: (1) Letters to Editors, Reviews and Books; (2) studies describing DOACs patient management during any kind of surgery different than oral surgery.

Only case–control studies were included in the meta-analysis: control groups were composed of either healthy patients or patients taking vitamin K inhibitors.

Outcome measures

The main outcome was the frequency of postoperative bleeding, defined as any kind of bleeding occurring immediately after surgical procedures or up to 7 days after surgery.

The primary independent variable was the type of anticoagulants taken by the patients; the secondary independent variable was the postoperative bleeding event.

Information sources and search strategy

The literature search for the present systematic review was conducted at PubMed, Scopus, Web of Science and Cochrane Library up to 18 August 2017.

The search strategy used a combination of different Medical Subject Headings (MeSH) terms and keywords in the four databases, and is summarized in Table 1.

The additional filter ''Language: English'' was used.

Study selection

Studies were selected in two-stage screening by two independent reviewers. The first-stage screening of titles and abstracts was carried out to eliminate irrelevant articles or articles that did not meet the inclusion criteria. At the second-stage screening of full texts, the study eligibility was verified. The level of agreement between the two reviewers was calculated using Kappa statistics for the first- and second-stage screening; disagreements about inclusion or exclusion of studies were resolved by consensus.

Data collection process/data items

Data were extracted based on the general study design (author and year of publication, country, study design) and study characteristics (number of cases, age, sex, anticoagulant type, modification of anticoagulant dosage before surgery, type of surgery, test group peri- or postoperative bleeding and measurements used to stop the bleeding).

Risk of bias in individual studies

The quality and risk of bias of all included studies were independently assessed by

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