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Assessing an oral surgery specific protocol for patients on direct oral anticoagulants: a retrospective controlled cohort study

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Abstract. Chronic therapy with the new direct oral anticoagulants (DOACs) poses new challenges for dental practitioners assessing the risk versus benefit of cessation versus non-cessation of anticoagulant therapy for dentoalveolar procedures. A retrospective controlled cohort study was designed to evaluate a non-cessation protocol for patients taking DOACs in the setting of dental extractions. A records review covering the period 1 January 2016 to 31 December 2016 identified 43 patients on DOAC therapy; 53 dentoalveolar procedures were performed under local anaesthesia, of which 15 included varying degrees of peri-procedural cessation. A control group of 50 patients on uninterrupted warfarin therapy undergoing 59 dentoalveolar procedures was identified. The incidence, severity, and timing of bleeding events were recorded for each group. Four (10.5%) minor bleeding events were recorded in the non-cessation DOAC group and nine (15.3%) minor bleeding events in the warfarin group. No bleeding events were recorded in the DOAC cessation group. Comparison of the incidence of bleeding events between the non-cessation DOAC group and the warfarin group showed no statistically significant difference (odds ratio 0.65, $P = 0.56$). Within the limitations of this study, dental extractions in the context of continuing DOAC therapy can be performed safely provided extra local haemostatic measures are applied.

Key words: direct oral anticoagulants; DOAC; novel oral anticoagulants; NOAC; dentoalveolar surgery.

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Anticoagulant therapy remains the recommended treatment for the prevention of thromboembolic events in at-risk patients. Since the 1950s, the most common long-term oral anticoagulant used has been a vitamin K antagonist, warfarin. However, warfarin is associated with numerous food–drug and drug–drug interactions and requires frequent monitoring via the

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international normalized ratio (INR) to ensure patients are receiving a therapeutic dose.

A new generation of anticoagulants, also referred to as direct oral anticoagulants (DOACs) have been developed to provide an alternative to the perceived drawbacks of warfarin, offering more predictable pharmacokinetics and pharmacodynamics and eliminating the need for routine dose titration. These include dabigatran, apixaban, and rivaroxaban. Dabigatran is a direct thrombin inhibitor, whereas apixaban and rivaroxaban are both factor Xa inhibitors.

In Australia, all three of these DOAC medications have been subsidized by the Australian government through the Pharmaceutical Benefits Scheme since September 2013, for the prevention of thromboembolic events in non-valvular atrial fibrillation (AF) and for venous thromboembolism (VTE) prophylaxis[1].

The anticoagulation efficacy and safety of these medications compared to warfarin have been shown to be favourable; rates of spontaneous cerebral or gastrointestinal bleeding have been similar or lower in phase III trials of these medications for the management of non-valvular AF and VTE prophylaxis and treatment[2–4].

DOACs have markedly different pharmacokinetic profiles to vitamin K antagonists. Peak plasma concentrations of dabigatran are achieved within 2–3 h and of factor Xa inhibitors (apixaban and rivaroxaban) within 3–4 h. Similarly, the half-lives of all three DOACs described vary between 10 h and 17 h[5–7]. This presents a dilemma in the peri-procedural management of these medications, as the quick onset and offset of the anticoagulation effects of these drugs raise the possibility of a more straightforward cessation protocol when compared to ceasing warfarin. Warfarin has a considerably longer half-life and may remain at a subtherapeutic dose once recommenced, potentially leaving the patient in a prothrombotic state[8]. Another key consideration is the lack of readily available reversal agents for DOACs. Recently, effective reversal of the targeted anticoagulants has been demonstrated for idarucizumab in the case of dabigatran and andexanet alfa in the case of factor Xa inhibitors[9,10], but only idarucizumab has been approved by the Australian Therapeutic Goods Administration for therapeutic use in Australia.

Currently, surgical guidelines focus on interruption of the DOAC peri-procedurally[6,11,12]. Within the context of oral surgery, however, the lower likelihood of encountering major vessels, direct access to potential bleeding sites, as well as a similar bleeding profile to warfarin, has led to the establishment of several best practice guidelines for the removal of teeth based on not ceasing the medications[13–15].

Clinical evidence and trials are growing. At the time of writing, a number of small case–control studies and case series had been published, examining both interrupted and uninterrupted peri-procedural protocols, in patients taking DOACs undergoing dental extractions[14,16,17] and implant therapy[18–20]. This retrospective study aimed to add to this growing body of evidence.

A non-cessation protocol for DOACs similar to that for warfarin, for use in patients undergoing extractions, was established at the Royal Dental Hospital of Melbourne at the beginning of 2016, based on the similar bleeding profiles of DOACs and warfarin in phase III trials (ARISTOTLE, ROCKET-AF, RE-LY)[2–4]. The protocol applied was similar to one recommended in the Australian therapeutic guidelines for warfarin for an INR between 2.2 and 4[21]. Clinicians were advised to apply the non-cease DOAC protocol for all patients unless advised otherwise by the patient's medical practitioner, or where concerns about comorbidities such as dual anticoagulation or significant renal disease existed, in which case liaising with the patient's medical practitioner was also recommended prior to treatment. The protocol utilized is outlined in Table 1.

The purpose of the present study was to explore the incidence of postoperative bleeding in patients on DOACs following a non-cessation protocol during extractions, and to assess whether this protocol compares favourably against an already established and accepted non-cessation protocol for patients undergoing extractions on long-term warfarin therapy.

Table 1. Protocol for extractions in patients on chronic DOAC therapy.

Single or multiple (up to 4) tooth extractions, or a single surgical extraction (for all patients, including those who ceased and those who did not cease DOAC therapy)
Following extraction of the teeth: Application of a topical haemostatic agent such as a gelatin sponge (Gelfoam), or an oxidized cellulose ribbon (Surgicel), along with Individual suturing of each extraction site
More than 4 extractions or multiple surgical extractions:
Where more than 4 extractions or multiple surgical extractions were required, clinicians were advised to seek the advice of the oral and maxillofacial surgery department and/or liaise with the patient's general physician to determine the risk profiles of staging the extractions versus cessation of the anticoagulant
Postoperative medication
4.8% tranexamic acid mouthwash to be used four times daily for 2 minutes
Follow-up
A 2-day follow-up or phone call and, where possible, a 2-week postoperative appointment or call was to be organized to assess any delayed bleeding events
Patients were also given an emergency number to call if they experienced any complications

DOAC, direct oral anticoagulants.

Materials and methods

This study was approved by the University of Melbourne Health Sciences Human Ethics Sub-Committee.

The investigators designed a retrospective controlled cohort study to compare the primary outcome of postoperative bleeding amongst patients who had undergone extractions while on DOAC therapy against a control group of patients who had undergone extractions while on warfarin.

A review of the records of patients over the age of 45 years who had undergone an extraction under local anaesthesia at the primary care and oral and maxillofacial surgery departments of the Royal Dental Hospital of Melbourne was conducted, covering the period 1 January 2016 to 31 December 2016. Extractions within these departments are performed predominantly by general dentists on an outpatient basis.

Three patient cohorts were identified from this review: patients who had undergone dental extraction while on chronic DOAC therapy (further stratified into those who ceased therapy and those who did not) and a control group of patients who had undergone dental extractions on chronic warfarin therapy without peri-procedural cessation.

Patients were eligible for study inclusion if they were at least 45 years old at the time of the procedure and had at least one tooth extraction under local anaesthesia during chronic DOAC (rivaroxaban, apixaban, dabigatran) or uninterrupted warfarin anticoagulant therapy between 1 January 2016 and 31 December 2016. Patients were excluded from the analysis if records were inaccessible or incomplete, or if follow-up was not recorded for at least 1 week and the occurrence of postoperative bleeding could not be determined via further clinical or phone review.

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