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Tranexamic acid to reduce bleeding after dental extraction in patients treated with non-vitamin K oral anticoagulants: design and rationale of the EXTRACT-NOAC trial

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Abstract

Bleeding after dental extraction in patients treated with non-vitamin K oral anticoagulants (NOAC) may lead to unplanned reinterventions and interruption of anticoagulation, thereby exposing patients to a risk of thromboembolism. We have designed a study (EXTRACT-NOAC) to investigate whether tranexamic acid (TXA) mouthwash decreases bleeding after extraction in such patients. The study is a randomised, double-blind, placebo-controlled trial. We plan to randomise 236 patients listed for dental extraction and treated with NOAC to 10% TXA mouthwash or placebo. Patients are instructed to use the mouthwash before the dental extraction, and three times a day for three days thereafter. The primary outcome is oral bleeding. Secondary outcomes include type of bleeding, procedural bleeding score, number of reinterventions after oral bleeding, and number of interruptions in NOAC treatment. Any bleeding from sources other than the mouth, and thrombotic events, are recorded as safety outcomes. Patients are followed-up for seven days. This study will provide evidence to guide the management of patients taking NOAC who need teeth extracted.

Keywords: Dental extraction; Non-vitamin K oral anticoagulants; Bleeding; Tranexamic acid

Introduction

Bleeds are common after dental extraction in patients taking oral anticoagulants, such as vitamin K antagonists (VKA) and non-vitamin K oral anticoagulants (NOAC).[1] To prevent bleeding, oral anticoagulants can be interrupted before dental procedures. Bleeding may also lead to unscheduled interruption of anticoagulants and temporary interuption puts the patients at risk of thromboembolic events.[2,3] Optimal management of anticoagulants is therefore crucial to balance the risk of bleeding and of thromboembolism.

Managing VKA is not simple because these drugs have a long half-life, some drug interactions, and are influenced by dietary vitamin K intake. Routine coagulation monitoring of patients taking them is therefore required. For patients having teeth extracted it is current practice to continue VKA,

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provided that the international normalised ratio is within the therapeutic range, as this confers less risk of bleeding than discontinuing or altering the dose.[4]

Since the introduction of NOAC, the number of patients treated with them has steadily increased. The perioperative management of patients on NOAC is easier than that of patients taking VKA, because of the shorter half-life of NOAC. However, the risk of mucosal bleeding is higher in patients taking NOAC than in those taking VKA.[5] Bleeding after extraction is a particular concern in patients treated with NOAC, because the oral mucosa is damaged during dental extraction. To minimise the risk of bleeding, the European Heart Rhythm Association advises that extractions are planned for when the concentration of NOAC in the blood is lowest, which can be achieved by letting the patient skip a dose on the morning of the extraction. With this approach, the risk of early bleeding after extraction is similar in patients taking NOAC and those taking no anticoagulant, but the risk of delayed bleeding is still higher for those taking NOAC.[6] The question remains how to reduce the risk of delayed bleeding in patients taking NOAC.

As well as for the management of oral anticoagulants, haemostatic agents are essential to minimise bleeding. Tranexamic acid (TXA) is an attractive haemostatic agent for local application during dental procedures because of its efficacy in reducing bleeding and its low systemic absorption.[7] The use of TXA mouthwash effectively decreases bleeding after dental extraction in patients treated with VKA.[8,9] Its use in patients taking NOAC, however, has not been studied yet to our knowledge. This study was set-up therefore to assess whether TXA mouthwash reduces bleeding after dental extraction in patients who are being treated with NOAC.

Patients and methods

The EXTRACT-NOAC study is a randomised, double-blind, placebo-controlled, investigator-initiated, clinical trial (ClinicalTrials.gov ID: NCT03413891). The Medical Ethics Committee Research UZ/KU Leuven approved the study in July 2017. Recruitment started in February 2018.

Patients and randomisation

Patients are eligible if they are treated with a NOAC (edoxaban, apixaban, rivaroxaban, or dabigatran), are listed for a dental extraction, and are older than 18 years. Exclusion criteria include pregnancy, lactation, or any condition that carries an increased risk of harm in case of participation (Table 1). Subjects provide informed consent before any study-related procedures. They are randomised using an interactive web response system to TXA or placebo mouthwash. All patients, treating surgeons, and investigators are unaware of the randomisation.

Table 1
Inclusion and exclusion criteria of the EXTRACT-NOAC trial.

≥18 years criteria	<18 years
Listed for dental extraction	Known allergic reaction to tranexamic acid
Treated with a NOAC: edoxaban, apixaban, rivaroxaban, or dabigatran	Pregnancy or lactation
No morning NOAC dose on the day of dental extraction	Having any condition that - as judged by the investigator - would place the subject at increased risk of harm if he/she participated
Informed consent	

Table 2
Definitions of oral bleeding events.

	Definition
Degree of severity:	
Major	Oral bleeding events requiring blood transfusion, hospitalisation or resulting in death.
Clinically relevant non-major	Oral, non-major bleeding events requiring unplanned medical contact or additional haemostatic measures (except for gauzes), with or without surgical reintervention.
Minor	Oral bleeding events such as bleeding requiring the use of additional gauzes, blood on the pillow, and clear red bleeding when spitting out the mouthwash.
Timing:	
Early	Oral bleeding that occurred after the extraction up to and including day 1 after dental extraction.
Delayed	Oral bleeding events that occurred between day 2 and day 7 after dental extraction.

Intervention

The study drug is 10% TXA mouthwash 1 g/10 ml or a matching placebo, and the mouthwash is packed into oral syringes of 10 ml. The mouthwash-containing syringes are produced by the Leuven Centre for Clinical Pharmacology, UZ Leuven, Belgium. The placebo mouthwash is water containing 2.5 ml cherry flavour/smell (45%), to mimic the flavour and smell of TXA mouthwash. At randomisation, patients are assigned to a drug kit containing 10 syringes of the study drug. The first application of the study mouthwash is immediately before the tooth is extracted. After extraction, it is used three times a day for three days, starting on the day after extraction.

Outcomes

The primary outcome is any oral bleeding up to day 7 after extraction. Oral bleeding is defined in three categories as previously published (Table 2).[6] Major oral bleeding is an event that requires blood transfusion or admission to hos-

Table 3
Primary, secondary and safety outcome variables.

	Outcome
Primary	Any oral bleeding
	Major oral bleeding
	Clinically relevant oral bleeding
	Minor oral bleeding
Secondary	Early oral bleeding events
	Delayed oral bleeding events
	Procedural bleeding score
	Reinterventions after oral bleeding
	Interruptions to NOAC treatment
Safety	Occurrence and number of any non-oral bleeding event
	Occurrence and number of any thrombotic event

pital, or results in death. Clinically relevant oral bleeding is not a major event and does not require unplanned medical contact with any health care professional or additional haemostatic measures (except for gauzes), with or without surgical reintervention. Reinterventions are defined as any procedure required in the oral cavity by a health care professional for the treatment of bleeding, except for rinsing the extraction socket with saline. Other oral bleeds, such as those that require additional gauzes, blood on the pillow, and fresh blood when spitting out the mouthwash, are classified as minor oral bleeds.

The primary outcome deliberately includes minor oral bleeds, because these bleeds may lead to discontinuation of the NOAC and the subsequent risk of thromboembolism. Additionally, oral bleeding is also categorised as early or delayed. Early bleeding is defined as any oral bleed up to 24 hours after extraction. Delayed bleeding is defined as any oral bleed between days 2 and 7 after extraction.

Secondary outcomes include the number of minor, clinically relevant, and major bleeds, early or delayed, the number of reinterventions after an oral bleed, and the number of unplanned interruptions of NOAC (Table 3). Any non-oral bleeds and thrombotic events, including myocardial infarction, stroke, systemic embolism, and venous thromboembolism, before the end of the study follow-up, are recorded as safety outcomes.

Study procedures

Periprocedural management

The perioperative management of patients treated with NOAC is to skip the NOAC dose on the morning of dental extraction, in agreement with the European Heart Rhythm Association.[10] After informed consent has been give, personal data, medical history, and data on smoking, alcohol consumption, and other drug use, are recorded.

Immediately before dental extraction, patients are instructed to rinse the mouth gently with 10% TXA 10 ml or placebo mouthwash for one minute before spitting it out. During dental extraction, the following information is recorded: indication for extraction, intraprocedural bleeding score (Visual Analogue Scale ranging from 0-10), tooth numbers of extracted teeth, and surgical techniques used. Data on the surgical technique include if there is suturing, burring, use of haemostatics (such as surgical sponges) and use of prophylactic oral antibiotics. After dental extraction, patients are monitored for half an hour to assure adequate haemostasis.

Management after extraction, and follow-up

Patients are instructed to rinse the mouth with the assigned mouthwash three times a day for three days, starting the day after extraction. They are given instructions on how to stop minor oral bleeding and are asked to record any bleeds. The NOAC is restarted on the day after the extraction, unless there are issues with haemostasis. Two and seven days after the extraction, patients are contacted by phone by investigators (who are unaware of the allocated treatment) to assess patients' compliance with the study protocol, occurrence of any oral bleeding, and safety outcomes (Fig. 1).

Statistical analysis

The null hypothesis states that there is no difference in the amount of oral bleeding between patients given the TXA mouthwash or the placebo mouthwash. Based on a pilot study on bleeding complications after dental extraction in patients treated with NOAC, the rate of the primary outcome (the occurrence of any oral bleeding) was estimated to be about 30% in the placebo group.[6] We estimated a reduction in absolute risk of 15% in the TXA group, which implies an expected incidence of 15%. To detect a significant difference in risk of bleeding between the TXA and placebo treatment, 118 patients in each group, or 236 patients in total, are required. The confidence level of the study is set to 95% and power to 80%.

The primary analysis will consist of the intention-to-treat group - all randomised patients who had at least one dose of the study mouthwash. In addition, we will do a sensitivity analysis of the per-protocol population – that is, all subjects with no major deviations from the protocol who complied with the assigned treatment by at least 80%. The overall significance level is set at 5% (two-tailed) $p = 0.05$.

The primary outcome – that is, the occurrence of bleeding up to day seven - will be analysed in terms of a difference in risk between the two treatment groups. The secondary endpoints will be compared using Fisher's exact test or the chi squared test, depending on the number of events.

An interim analysis with blinded re-estimation of the sample size is planned after 100 patients have been included. All data about the primary endpoint will be passed on to an independent statistician. The aim of this interim analysis is to estimate the incidence of oral bleeding and to recalculate the sample size based on this newly-estimated incidence of oral bleeding.

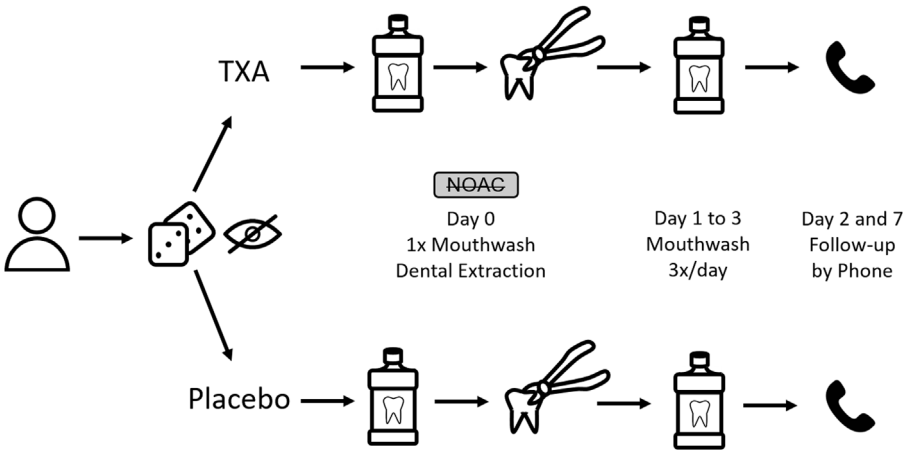

Fig. 1. Study design of the EXTRACT-NOAC study. After informed consent, patients are randomised to tranexamic acid mouthwash or to placebo mouthwash. The mouthwash is used immediately before dental extraction (day 0), and after dental extraction three times a day for three days (days 1-3). Patients are contacted on day 2 and day 7 after dental extraction to assess all outcomes and compliance.

Table 4
Characteristics of the non-vitamin K oral anticoagulants.

	Rivaroxaban (Xarelto®, Bayer)	Apixaban (Eliquis®, Bristol-Myers Squibb)	Edoxaban (Lixiana®, Daiichi Sankyo)	Dabigatran (Pradaxa®, Boehringer Ingelheim)
Working mechanism	FXa inhibitor	FXa inhibitor	FXa inhibitor	FIIa inhibitor
Standard dose in atrial fibrillation	20 mg qd	5 mg bd	60 mg qd	150 mg (EU) bd
Reduced dose	15 mg qd	2.5 mg bd	30 mg qd	110 mg bd
Half-life (h)	5-9	12	10-14	12-17
Renal elimination (%)	35	27	35	80

qd = once daily, bd = twice daily.

Discussion

Bleeding after dental extraction is an important concern for patients taking oral anticoagulants. The optimal management of NOAC to minimise bleeding is unknown, and patients on NOAC may be more prone to mucosal bleeding after extraction than patients taking VKA.[5] In patients treated with VKA, TXA reduces the risk of periprocedural bleeding, but we know of no data for patients taking NOAC.[9] This trial was therefore designed to investigate the efficacy of TXA mouthwash to reduce oral bleeding after dental extraction in these patients.

Two types of oral anticoagulants

The most common indications for oral anticoagulants include the prevention of stroke in patients with atrial fibrillation, the treatment and prevention of pulmonary embolism and deep venous thrombosis, and the prevention of thrombosis of a mechanical heart valve. VKA were the gold standard for many years, but recently NOAC have become the recommended treatment. Four NOAC are currently approved: rivaroxaban (Xarelto®, Bayer), apixaban (Eliquis®, Bristol-Myers Squibb), edoxaban (Lixiana®, Daiichi Sankyo), and dabigatran (Pradaxa®, Boehringer Ingelheim) (Table 4).[11–14]

VKA inhibit the hepatic synthesis of clotting factors II, VII, IX and X, while NOAC specifically inhibit factor Xa (rivaroxaban, edoxaban, and apixaban) or factor IIa (dabigatran). In contrast to VKA, NOAC have a more rapid onset and cessation of action, fewer drug interactions, are not influenced by dietary intake of vitamin K, and do not require routine monitoring of coagulation.[11]

NOAC are as effective as VKA in the prevention of stroke in patients with atrial fibrillation, but have a superior overall safety profile.[11] A meta-analysis of the ROCKET-AF (rivaraxaban compared with warfarin), ARISTOTLE (apixaban compared warfarin), ENGAGE AF-TIMI 48 (edoxaban compared with warfarin) and RE-LY (dabigatran compared with warfarin) trials, has illustrated the overall favourable benefit:risk profile of NOAC compared with warfarin.[11] The use of NOAC resulted in significant reductions in mortality, stroke, and intracranial haemorrhage, and a similar rate of major bleeding, but a higher rate of gastrointestinal bleeding compared with warfarin.[11–15]

Management of NOAC

Data on the management of NOAC in patients having teeth extracted are limited.[16] The European Heart Rhythm Association advises that teeth should be extracted when the concentration of NOAC in the blood is least.[17] However, it can be complicated to list the extraction at the time of the day corresponding to this. A standardised pragmatic approach (skipping only the dose of NOAC on the morn-

ing of the procedure) regardless of the timing of extraction, drug regimen, or renal function, has been evaluated in a study involving patients taking NOAC and those not being anticoagulated.[6] There was no difference in procedural and early bleeding between these groups. Nevertheless, delayed bleeding between days one and seven after extraction was more common in patients taking NOAC than in those taking no anticoagulant. Similarly, an increase in bleeding during the first postoperative week after dental extraction in patients taking uninterrupted rivaroxaban was reported in a retrospective study by Hanken et al.[18] Patients treated with NOAC are also more susceptible to mucosal bleeding.[5] This is worrying, because damage to the oral mucosa during dental extraction is unavoidable. In addition, the combination of peak plasma concentrations of NOAC, and an immature coagulum at the extraction site, can trigger bleeding. Because of both the bleeding risk and the thromboembolic risk during the procedure, an optimal strategy to minimise bleeding after extraction is required.[3]

TXA mouthwash to reduce bleeding

TXA is an antifibrinolytic agent that reversibly inhibits plasminogen, and prevents plasmin from degrading fibrin. Originally, it was developed for the treatment of haemophilia and other bleeding disorders, and it is also indicated for the treatment of heavy menstrual bleeding. Nowadays, it is widely used to manage injured patients or patients having operations who are at risk of haemorrhage.[19] Over time, it has also started being used in oral surgery. A recent systematic review showed the considerable benefit of TXA as a local haemostatic agent for patients having dental extractions.[8]

The topical use of TXA mouthwash is of special interest for oral surgery because of its low systemic absorption. TXA 1 g given systemically leads to peak plasma concentrations of 7 μg/ml, with no detectable traces in the saliva, while topical 5% TXA 10 ml mouthwash resulted in low blood plasma concentrations (< 2 μg/ml) and therapeutic concentrations in the saliva (20). Consequently, topical TXA is considered safe, with no evidence of prothrombotic systemic adverse effects.[7,20]

The current trial will investigate if a three-day course of TXA reduces the amount of bleeding after extraction in patients treated with NOAC. A short period of treatment is attractive from an economical point of view. TXA mouthwash is also available in 10-dose packages, which is perfectly suitable for clinical practice: one dose before dental extraction, followed by three doses a day for three days. TXA is also a low-cost drug and is already on the market. For all these reasons, the efficacy of TXA mouthwash to reduce bleeding after dental extraction requires appropriate investigation in a randomised, placebo-controlled, study.

Conclusion

There is an unmet need for clinical data on how to minimise bleeding in patients taking NOAC who need to have teeth removed. The EXTRACT-NOAC trial investigates if TXA mouthwash reduces bleeding after extraction in these patients. The primary outcome is oral bleeding, but thromboembolic events are recorded as well. In the end, balancing the risk of bleeding and the risk of thromboembolism is critical. The results of this trial will help to optimise the periprocedural management of NOAC in patients who require dental extraction.

Ethics statement/confirmation of patients' permission

The Medical Ethics Committee Research UZ/KU Leuven approved the study in July 2017. Patients' permission was obtained before any study procedure.

Conflict of interest

No authors have any conflicts of interest with respect to the EXTRACT-NOAC study. Dr. Verhamme received grants and personal fees from Bayer Healthcare, grants and personal fees from Boehringer Ingelheim, Pfizer, BMS, Daiichi-Sankyo, Leo Pharma, and Portola and Medtronic outside the submitted work.

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