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Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing oral or dental procedures (Protocol)

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[Intervention Protocol]

Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing oral or dental procedures

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

We aim to assess the efficacy of antifibrinolytic agents for preventing bleeding complications in people on oral anticoagulants undergoing oral or dental procedures.

Secondary objectives are to assess if antifibrinolytic agents can eliminate the need for the discontinuation or a dose reduction of oral anticoagulants before and during oral or dental procedures.

BACKGROUND

Description of the condition

Oral and dental procedures are commonly performed and can be complicated by hazardous oral bleeding. People on continuous treatment with a vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs) are at increased risk of bleeding complications during and after these types of procedures.

Vitamin K antagonists

Vitamin K antagonists are the most commonly used anticoagulant drugs; they act by inhibiting the carboxylation of the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X, and of the proteins C and S (Mega 2015). They are used for the prevention and treatment of thrombosis in a number of cardiovascular conditions, such as atrial fibrillation, venous thromboembolism and prosthetic heart valves (Douketis 2012).
Therapeutic levels of VKAs are measured by the international normalised ratio (INR), which should be held within a narrow therapeutic range to prevent thromboembolism without introducing bleeding complications (Sime 2015; Douketis 2012; Perry 2007; Randall 2007). This can be challenging due to the variability in dose response among individuals and interactions with other drugs and food; it therefore requires frequent laboratory control (Ansell 2004). After establishing the individual risk pattern, individuals are assigned to either a low- or a high-intensity INR therapeutic range. Internationally, the low- and high-intensity therapeutic ranges are defined as INR levels between 2.0 and 3.0, and between

2.5 and 3.5, respectively (Ansell 2004).

An INR level above or below the threshold is associated with an increased bleeding or thromboembolic risk, respectively. In addition, the withdrawal of anticoagulant treatment may induce a rebound hypercoagulant state due to excessive thrombin generation (Ascani 1999; Cundiff 2008; Palareti 1996). This would increase the risk of thromboembolic events even further after VKA interruption (Ascani 1999; Cundiff 2008; Palareti 1996). In a review of literature including studies with trial designs ranging from controlled clinical trials to case reports, the overall incidence of significant postoperative bleeding in 950 individuals on anticoagulant treatment undergoing 2400 individual dental procedures was 1.3% (n = 12) (Wahl 2000). Seven of these individuals had higher INR levels than recommended. Of 526 individuals undergoing 575 dental surgical procedures (dental extractions, alveolar surgery and gingival surgery) with discontinuation of continuous anticoagulant treatment, 0.95% (n = 5) suffered serious embolic complications; four out of these five individuals did not survive (Wahl 2000).

Direct oral anticoagulants

Direct oral anticoagulants were developed as alternatives to VKAs. Major advantages of DOACs include fewer food and drug interactions, a short half life and fixed-dose anticoagulation without the need for periodic monitoring (Hussain 2016). The DOACs act by directly inhibiting activated clotting factors. Currently available DOACs include dabigatran, rivaroxaban and apixaban; dabigatran inhibits factor IIa (thrombin), and rivaroxaban and apixaban inhibit factor Xa (Adcock 2015). A recently published retrospective observational study compared 52 oral procedures in individuals under continued anticoagulant treatment with rivaroxaban (20 mg per day) with 285 oral procedures in individuals without any anticoagulant or antiplatelet treatment (Hanken 2016). The number of postoperative bleeding complications was significantly higher in the rivaroxaban group compared to the control group, with bleeding complications in 11.5% and 0.7% of the individuals respectively. All bleeding complications were manageable with local measures.

Perioperative management in oral or dental procedures

Fibrinolytic activity is particularly high in oral mucosa due to the fibrinolytic activity of saliva and the local production of tissue plasminogen activator (t-PA) which converts plasminogen into plasmin causing fibrin degradation (Sindet-Pedersen 1990). The use of antifibrinolytic agents could therefore enable the continuation of oral anticoagulant treatment in people undergoing oral or dental procedures, while limiting the risk of bleeding. It is especially interesting to note that for hours after mouth rinsing with tranexamic acid (TXA) mouthwash, TXA concentrations in saliva remain at a therapeutic level, while after oral administration, TXA concentrations in saliva remain undetectable (Sindet-Pedersen 1990).

Traditionally, the perioperative management of oral and dental procedures in anticoagulated individuals included interruption or dose reduction of anticoagulant treatment to prevent bleeding complications. Recent guidelines recommend to either continue VKAs with an additional 'prohemostatic intervention' or to stop VKAs two to three days before the procedure, depending on the thromboembolic and bleeding risks of the individual and the type of surgical procedure (Douketis 2012; Perry 2007; Randall 2007; Sime 2015). Evidence for both treatment regimens is scarce. According to the aforementioned guidelines, prohemostatic interventions include, for example, antifibrinolytic agents, sutures, oxidized cellulose or collagen sponges (Douketis 2012; Perry 2007; Randall 2007; Sime 2015).

Guidelines present the same recommendations for DOACs as for VKAs. These include either continuing treatment with local prehemostatic measures or discontinuing treatment before the procedure, after careful assessment of the bleeding risk and the thromboembolic risk respectively. In general, treatment with DOACs should be discontinued in cases of moderate or high bleeding risk, and treatment may be continued in cases with a low bleeding risk (Heidbüchel 2012; Heidbüchel 2013; Heidbuchel 2015; Randall 2015). Dental procedures associated with a low bleeding risk include the extraction of one to three teeth, periodontal surgery, incision of an abscess and implant positioning (Heidbuchel 2015). Considering the risk of fatal thromboembolism after the withdrawal of anticoagulant treatment in the perioperative phase, it is important to continue this treatment and to search for additional methods or agents to prevent bleeding complications. Antifibrinolytic therapy is a relatively cheap, safe and potentially effective therapy for preventing bleeding complications in oral and dental procedures (Forbes 1972; McCormack 2012; Olsen 2016; Sindet-Pedersen 1989). Current guidelines recommend the use of additional prohemostatic interventions in people on continuous oral anticoagulant treatment undergoing oral and dental procedures to minimise the bleeding risk. Current guidelines do not state clearly which additional prohemostatic intervention should be preferred.

Description of the intervention

The main precautions used to prevent perioperative bleeding in people on continuous anticoagulant treatment undergoing oral or dental procedures are prohemostatic interventions, including the previously mentioned antifibrinolytic agents, sutures, oxidized cellulose and collagen sponges (Douketis 2012; Perry 2007; Randall 2007). The most commonly used antifibrinolytic agents are TXA and epsilon aminocaproic acid (EACA). Antifibrinolytics prevent degradation of the fibrin clot which supports blood clotting. Antifibrinolytic agents can be administered topically as a mouthwash or systemically as oral or intravenous formulations (*see* table be-

low). There are currently no guidelines available on when antifibrinolytic treatment should be started and for how long treatment should be continued. In general, if TXA is used, it is given before the dental procedure and three- to four-times daily for one or two days after the procedure (Douketis 2012). In people with renal insufficiency, a dose reduction is necessary to ensure renal clearance. Antifibrinolytic agents are contraindicated if there is active venous or arterial thromboembolic disease.

Dosing of antifibrinolytic agents

Antifibrinolytic agent	Available strength	Dose (adults)	Dose (children)
TXA mouthwash	50 mg/ml	10 ml, 4-times-daily	≥ 1 year: 20 mg/kg bodyweight/ day in 2 to 3 doses per day
IV TXA	100 mg/ml slowly IV (1 ml/min)	500 mg to 1000 mg, 2-to 3-times-daily	≥ 1 year: 20 mg/kg bodyweight/ day in 2 to 3 doses per day
TXA tablets	500 mg	1 to 1.5 g, 2-to 3-times-daily	≥1 year: 20 mg/kg bodyweight/ day in 2 to 3 doses per day
IV EACA	250 mg/ml	Starting dose 4 g to 5 g slowly IV (more than 1 hour), followed by continuous infusion of 1 g/hour	100 mg/kg or 3 g/m² slowly IV during the first hour, followed by continuous infusion 33.3 mg/kg/ hour or 1 g/m²/hour
EACA tablets	500 mg and 1000 mg	Starting dose 4 g to 5 g, followed by 1 to 1.25 g/hour. Maximum dose 24 g per 24 hours	starting 100 mg/kg, followed by 3 g/m2 during the first hour, followed by 33.3mg/kg or 1 g/m² every hour, maximum 18 g/m² (600 mg/kg) in 24 hours

Abbreviations: EACA: epsilon aminocaproic acid; IV: intravenous; TXA: tranexamic acid.

How the intervention might work

The antifibrinolytic agents TXA and EACA act by binding reversibly to plasminogen and blocking the interaction of plasminogen with fibrin, thereby preventing degradation of the fibrin clot. The agent TXA is more potent than EACA (Pell 1973). Fibrinolytic activity is particularly high in oral mucosa due to the fibrinolytic activity of saliva and local t-PA production (Sindet-Pedersen 1990). Therefore, the inhibition of fibrinolysis with antifibrinolytic agents is a rational approach for limiting oral bleeding after surgery in people using oral anticoagulants.

Why it is important to do this review

The aim of this review is to analyse the evidence for the use of antifibrinolytic agents in people on continuous VKA or DOAC treatment undergoing oral or dental procedures. Given their low cost, high tolerability, effectiveness and safety, antifibrinolytic agents are an attractive alternative to prevent perioperative bleeding in oral surgery. If sufficient evidence is found to support the use of antifibrinolytic agents in people on continuous oral anticoagulant treatment undergoing oral and dental procedures, this treatment should become the standard therapeutic approach. Perioperative

continuous anticoagulant treatment may prevent the need for the discontinuation or a dose reduction of anticoagulant drugs, reducing the thromboembolic risk with potentially life-threatening outcomes. To our knowledge, no recent systematic review or meta-analysis on antifibrinolytic therapy in people on anticoagulants undergoing oral or dental procedures has been performed.

OBJECTIVES

We aim to assess the efficacy of antifibrinolytic agents for preventing bleeding complications in people on oral anticoagulants undergoing oral or dental procedures.

Secondary objectives are to assess if antifibrinolytic agents can eliminate the need for the discontinuation or a dose reduction of oral anticoagulants before and during oral or dental procedures.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials in people on anticoagulant treatment undergoing oral or dental procedures.

Types of participants

People of all ages on VKA or DOAC treatment undergoing oral or dental procedures. We will define the therapeutic range of VKAs as an INR between 2.0 and 4.0. Oral and dental procedures include surgery related to teeth (tooth extraction including third molar removal and implant placement), periodontal tissues, or soft tissues in the oral cavity. People using acetylsalicylic acid will not be included in this review, as the general approach for minor dental procedures in these individuals already includes continuation of acetylsalicylic acid without an increased risk of excessive bleeding (Douketis 2012; Zhao 2015).

Types of interventions

Intervention

The use of antifibrinolytic agents (TXA or EACA) to prevent perioperative bleeding in people on oral anticoagulant medication undergoing oral or dental procedures at any dose, mode of delivery (topical, oral or intravenous), frequency and duration of administration, whether started before, during or immediately after the intervention.

Comparator interventions

Placebo or no intervention or usual care with or without placebo. Usual care in this population includes discontinuation or dose reduction of oral anticoagulants perioperatively, or continuation of oral anticoagulants with additional local prohemostatic measures (e.g. suturing, local administration of fibrin glue or hemostatic gelatin sponge) except for local antifibrinolytic agents.

Types of outcome measures

Primary outcomes

1. Number of major postoperative bleeding episodes (defined as postoperative bleeding episodes requiring intervention*)
2. Side effects or other adverse events**

* Intervention is defined as any additional treatment or medical attention needed in addition to usual care to halt postoperative bleeding directly up to 10 days post surgery. Postoperative bleeding episodes include immediate postoperative bleeds (defined as bleeding within 24 hours after surgery), as well as delayed postoperative bleeds (defined as bleeding 24 hours to 10 days after surgery). Local pressure is the usual care used to halt bleeding; both clinically relevant (non-major) bleeding requiring medical attention (e.g. wound dressing or additional sutures) and major bleeding requiring transfusion of packed red blood cells.

**Side effects of antifibrinolytic agents are mainly gastro-intestinal and will only be considered clinically relevant if they lead to the discontinuation or a change of therapy.

Secondary outcomes

1. Number of minor postoperative bleeding episodes (defined as self-limiting, usually with local pressure, that does not require medical attention)
2. Number of immediate (less than 24 hours) and delayed (24 hours to 10 days) postoperative bleeding episodes requiring intervention
3. Any postoperative complication except bleeding (e.g. wound infection)
4. Change in haemoglobin level from baseline
5. Major bleeding, requiring transfusion of packed red blood cells
6. Bleeding duration (minutes, all types of bleeding minor and major)
7. Amount of postoperative blood loss (ml)
8. Number of thromboembolic complications

Search methods for identification of studies

Electronic searches

Search to be performed by the Cystic Fibrosis and Genetic Disorders Group

The Cystic Fibrosis and Genetic Disorders (CFGD) Group will identify relevant studies from the Group's Coagulopathies Trials Register.

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and the International Society on Thrombosis and Haemostasis. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Searches to be performed by the authors

In addition to the CFGD Group's search, we will search the databases Embase (covering journals from 1947 to 2016), *The Cochrane Library* (www.cochranelibrary.com/) and PubMed (www.ncbi.nlm.nih.gov/pubmed). We will search the Cochrane Database for Systematic Reviews (CDSR) as well as the Cochrane Central Register of Controlled Trials (CENTRAL). Furthermore, we will search the CINAHL database of nursing and allied health services (covering full texts from 1937 to 2016), trial registries and the open access Proquest dissertation database (pqdtopen.proquest.com/search.html), as well as the ongoing trial registers: ClinicalTrials.gov (www.clinicaltrials.gov/); and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/). The meeting abstracts published online by the American College of Clinical Pharmacy (ACCP; www.accp.com) from 1979 to 2016 will also be part of the search. We will also search for additional relevant publications in the online abstract books of the scientific meetings and congresses mentioned in the first paragraph of this section (Electronic searches). Please refer to an appendix for details of the search strategies (Appendix 1). We will not apply any date or language restrictions to the search. To search the databases, we will use platforms available through the Utrecht University Library.

Searching other resources

In an attempt to find additional relevant trials, we will screen the reference lists of all included trials by hand.

Data collection and analysis

Selection of studies

Two authors (EE content area expert, KG content area expert and supervising author) will independently screen titles and abstracts of all articles obtained through the searches and identify abstracts of trials that appear to be potentially relevant. Full texts will be obtained for potentially relevant abstracts and two authors (EE, KG) will independently assess these for inclusion based on the previously described selection criteria. A third author (RG) will verify trial eligibility. For this purpose we will use a separate data collection form for assessing trial eligibility. Multiple reports of the same trial will be identified by comparing authors of the reports, trial dates, trial durations, number of participants, details on the interventions and location and setting of the reported trials. When multiple reports on one or more trials are identified these reports will be linked together. A third author (RS content area expert, methodologist) will verify the assessment of trials identified for inclusion. We will resolve any disagreement by discussion between three authors (EE, KG, RS). When necessary, to clarify the eligibility of certain trials, we will try to request further information for the original authors. Duplicate records of the same reports will be removed using reference manager software (RefMan® 2010). We will record the articles retrieved from the searches of the databases in the Review Manager (RevMan) software (RevMan 2014). We will list the excluded trials, except if obviously not fulfilling the selection criteria of this review, and we will state the primary reason for exclusion.

Data extraction and management

Two authors (EE, KG) will independently extract data from published reports using a data extraction form containing the characteristics of the included trials and trial participants, all outcome measures and a risk of bias table. We will prepare the data extraction form using the general template for 'Summary of findings' tables and a Cochrane checklist of items to consider in data collection or data extraction (Higgins 2011a), which will be authorised by all authors. A third author will verify the data extraction of trials identified for inclusion (RS). If there are any disagreements, we plan to resolve these by discussion between three authors (EE, KG, RS). If possible, we will extract the primary outcome measure of the number of postoperative bleedings needing intervention from the included trials. When necessary, to clarify data from certain trials, we will try to request further information for the original authors.

Assessment of risk of bias in included studies

We will assess the methodological quality of the included trials by using a risk of bias table that includes judgments of the ade-

quacy of the sequence generation (selection bias), allocation concealment (selection bias), blinding of the outcome assessments (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (Higgins 2011a). Two authors (EE, KG) will independently complete this table for each included trial. We will resolve any disagreements by discussion between three authors (EE, KG, RS). We will rate the risk of bias for each domain as low, unclear or high and summarise this information in a 'risk of bias' plot.

Measures of treatment effect

The treatment effect is the proportion of participants in the intervention group with postoperative bleedings needing treatment (immediate as well as delayed postoperative bleedings will be combined), compared to those in the control group. For meta-analysis, we will express this treatment effect as an absolute risk. We can also convert this measure to a number-needed-to-treat (NNT), after calculating the risk difference between the two groups. The NNT will be useful for better interpretation of the results of our meta-analysis. In the event that there are included trials where no events are observed in both groups, these trials will be added to the forest plot.

Formula: NNT = 1 / risk difference.

Should individual participants experience more than one event (e.g. postoperative bleeding needing intervention, side effects or adverse events), we will calculate the rate of events in the two groups by dividing one by the other, expressed as rate ratios with their corresponding 95% confidence intervals (CIs) and analysed using Poisson regression. Likewise, we will express the difference of the effect measures for the secondary outcomes (e.g. the number of minor postoperative bleedings, postoperative complications except bleeding, major bleeding requiring blood transfusion and the need for additional prohemostatic treatment) between the intervention group and the control group as combined absolute risks. For other secondary outcomes (e.g. change in haemoglobin level, duration of bleeding, amount of postoperative blood loss and additional prohemostatic treatment requirement), we will calculate the mean difference (MD) with corresponding 95% CIs between the two groups. If necessary, we will transform the outcome measurements for these continuous data in different studies to the same scale (i.e. bleeding duration in minutes, amount of blood loss in ml) (Deeks 2011).

Unit of analysis issues

We will include trials with non-standard randomised controlled designs, since these study designs can be feasible to answer the research question. Including data of such trials can also increase the power for meta-analysis.

Cross-over trials

We will include cross-over trials since participants may have an indication for multiple identical dental or oral procedures within a certain study period. In a cross-over trial, all participants are randomised to the sequence in which they will receive treatments. Every participant receives both the intervention and the control treatment, which allows the determination of the best treatment or preference for an individual participant (Higgins 2011b). We will analyse data from cross-over trials in the meta-analysis as if they were parallel group trials.

Multiple randomisations

Participants may be randomised on multiple occasions in a trial due to revisits for the same or a similar dental or oral procedure. In this case, participants do not necessarily undergo both treatments. We will account for this issue by using the number of participants rather than the number of interventions as the unit of analysis.

Studies with multiple treatment groups

If included clinical trials randomise participants to one of several intervention groups, only the groups where the intervention consists of the administration of antifibrinolytic agents to prevent bleeding in oral surgery and the comparison groups with placebo, no intervention or usual care with or without placebo will be included in the meta-analysis using the same treatment effect measure as in the included parallel group trials. If possible and if the inclusion criteria are met, we will present the effect measure separately in the meta-analysis if more than two groups are relevant with regard to differences in the administration of antifibrinolytic agents, using a proportional part of the comparison group, to allow for any subgroup analyses (Higgins 2011b).

Cluster-randomised trials

If we include cluster-randomised trials while assessing the risk of bias, we plan to pay special attention to the possibility of: recruitment bias; baseline imbalances; loss of clusters; incorrect analysis; herd effect; and contamination (Higgins 2011c). In the meta-analysis we plan to use the same treatment effect measure as in the included parallel group trials if the original analysis properly accounts for the cluster design, based for example on a multilevel model or generalised estimating equations (GEEs). We will seek statistical advice if needed.

Dealing with missing data

Possible sources of missing data are: missing outcomes; selective or incomplete reporting; and lack of intention-to-treat (ITT) analysis. We will contact the original investigators to request missing data whenever possible. If possible, we will address the potential

impact of missing data on the findings in the 'Discussion' section of our final review by using sensitivity analysis (Higgins 2011b).

Assessment of heterogeneity

Expected differences in the specific interventions and participant characteristics will give rise to clinical heterogeneity between the included trials. We will consider a visual inspection of the forest plot to see whether the CIs overlap. In addition, significant statistical heterogeneity arises from methodological differences between studies (Deeks 2011). To quantify inconsistency between trials, we will calculate the I^2 statistic to describe the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins 2003).
The interpretation of the I^2 values will be as follows (Higgins 2003):
0% to 40% indicates unimportant levels of heterogeneity;
30% to 60% indicates moderate heterogeneity;
50% to 90% indicates substantial heterogeneity;
75% to 100% indicates considerable heterogeneity.

Assessment of reporting biases

To address reporting bias, the literature searches will be as comprehensive as possible so as to prevent missing trials that meet the eligibility criteria. We will search several clinical trials registries for this purpose (*see* Electronic searches). We plan to construct a funnel plot only if we include enough trials (10 or more). When asymmetry occurs, we will consider the possibility that this provides evidence of small-study effects and publication bias as only one of the possible explanations (Sterne 2011). We will attempt to understand the source of any small-study effects and consider their implications in sensitivity analyses. We will address the potential impact of reporting bias on the findings in the 'Discussion' section of our final review (Higgins 2011b).

Data synthesis

We assume that included trials use different outcome definitions of postoperative bleeding. If possible, we will try to distillate the number of postoperative bleedings needing intervention and use this outcome measure will be used for meta-analysis. We will combine all types of interventions with antifibrinolytic agents. Given that we expect heterogeneity between the trials, due to different outcome measures and differences in the administration of antifibrinolytic agents and the use of co-interventions, we will use a random-effects model for meta-analysis. If we cannot undertake a meta-analysis because of too much heterogeneity between the included trials, we will only enter extracted data in a 'Summary of findings' table and provide a narrative synthesis.

Subgroup analysis and investigation of heterogeneity

If we include sufficient trials, we will conduct the following planned subgroup analyses to allow for subgroup analysis as a means of investigating heterogeneous results, to answer specific questions about particular participant groups, types of interventions and types of trials (Deeks 2011).

1. Antifibrinolytic agents used: TXA versus EACA.
2. Administration form of antifibrinolytic agents: topical versus systemic.
3. Different outcome definitions of perioperative bleeding: clinically significant versus minor versus major postoperative bleedings; and immediate versus delayed postoperative bleedings.
4. INR levels within the therapeutic range versus INR levels below or above the thresholds of the therapeutic range.
5. Timing of the antifibrinolytic intervention: before, during or after the oral or dental procedure.

Sensitivity analysis

If we include sufficient trials in the meta-analysis, we will perform sensitivity analyses aimed at determining whether conclusions are robust regarding the following.

1. Risk of bias: by excluding high risk of bias studies.
2. Publication type: by excluding abstracts whose results cannot be confirmed in subsequent publications versus full texts papers.
3. Methodological aspects: by excluding non-blinded randomised controlled trials and by excluding non-standard designs, including versus excluding trials with missing data.

We will include in the final review other issues suitable for sensitivity analysis that we identify during the review process based on different decisions we make. If any sensitivity analysis identifies particular decisions or missing information that greatly influences the findings of the review, we will deploy greater resources to try and resolve uncertainties and obtain extra information from the original authors. If we cannot achieve this, we will interpret the results with a certain degree of caution, and state this in the 'Discussion' section (Deeks 2011). We will report the sensitivity analyses by producing a summary table.

Summary of findings table

We will present the findings of the included trials in a 'Summary of findings' table that will contain the primary outcome measures and the secondary outcome measures, a measure of the typical burden of these outcomes (illustrative risk on control intervention), the absolute and relative magnitude of the effect (risk ratio (95% CI) and absolute risks), the numbers of participants and studies addressing these outcomes, risk of bias assessment, source of any external information ('assumed risk' column) and quality assessment for each outcome measure according to the GRADE approach (high, moderate, low or very low) and space for comments (Schünemann 2011a; Schünemann 2011b).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

PubMed (no restriction on publication data)

("surgery, oral"[MeSH Terms] OR "oral surgical procedures"[MeSH Terms] OR "tooth extraction"[MeSH Terms] OR "Dentistry, Operative"[MeSH] OR "molar"[MeSH Terms] OR "oral surgery"[tiab] OR "oral surgical procedures"[tiab] OR dental[tiab] OR tooth[tiab] OR "operative dentistry"[tiab] OR molar[tiab] OR dentoalveolar[tiab] OR orthognathic[tiab] OR periodontal[tiab])
AND
("anticoagulants"[MeSH Terms] OR "anticoagulants"[Pharmacological Action] OR "warfarin"[MeSH Terms] OR "phenprocoumon"[MeSH Terms] OR "acenocoumarol"[MeSH Terms] OR "coumarins"[MeSH Terms] OR anticoagulants[tiab] OR anticoagulant[tiab] OR anticoagulation[tiab] OR anticoagulated[tiab] OR "vitamin k antagonist"[tiab] OR "anti-vitamin k"[tiab] OR "antivitamin k"[tiab] OR "anti vitamin k"[tiab] OR "acquired disorder of coagulation"[tiab] OR "acquired coagulation disorder"[tiab] OR "acquired coagulopathy"[tiab] OR "acquired coagulopathies"[tiab] OR VKA[tiab] OR warfarin[tiab] OR phenprocoumon[tiab] OR acenocoumarol[tiab] OR coumadin[tiab] OR coumadins[tiab] OR coumarin[tiab] OR coumarins[tiab] OR "new oral anticoagulant"[tiab] OR "newer oral anticoagulant"[tiab] OR NOAC[tiab] OR "non-vitamin k antagonist"[tiab] OR "non-vitamin-k-antagonist"[tiab] OR "non-vitamin k dependent antagonist"[tiab] OR DOAC[tiab] OR "direct oral anticoagulant"[tiab])
AND
("antifibrinolytic agents"[MeSH Terms] OR "antifibrinolytic agents"[Pharmacological Action] OR "tranexamic acid"[MeSH Terms] OR "aminocaproic acid"[MeSH Terms] OR antifibrinolytic[tiab] OR tranexamic[tiab] OR cyclokapron[tiab] OR cyklokapron[tiab] OR eaca[tiab] OR "aminocaproic acid"[tiab] OR amicar[tiab] OR TXA[tiab])

Embase (no restriction on publication data)

('oral surgery'/exp OR 'oral surgery' OR 'dental procedure'/exp OR 'dental procedure' OR 'tooth'/exp OR 'tooth' OR 'orthognathic surgery'/exp OR 'orthognathic surgery' OR 'oral surgery':ab,ti OR 'oral surgical procedures':ab,ti OR dental:ab,ti OR tooth:ab,ti OR dentoalveolar:ab,ti OR orthognathic:ab,ti)
AND
('anticoagulant agent'/exp OR 'anticoagulant agent' OR 'anticoagulation'/exp OR 'anticoagulation' OR 'anticoagulant therapy'/exp OR 'anticoagulant therapy' OR 'coumarin derivative'/exp OR 'coumarin derivative' OR anticoagulation:ab,ti OR anticoagulant:ab,ti OR anticoagulants:ab,ti OR anticoagulated:ab,ti OR coumarin:ab,ti OR coumarins:ab,ti OR coumadin:ab,ti OR coumadins:ab,ti OR warfarin:ab,ti OR phenprocoumon:ab,ti OR acenocoumarol:ab,ti OR 'vitamin k antagonist':ab,ti OR 'anti-vitamin k':ab,ti OR 'antivitamin k':ab,ti OR 'anti vitamin k':ab,ti OR 'acquired disorder of coagulation':ab,ti OR 'acquired coagulation disorder':ab,ti OR 'acquired coagulopathy':ab,ti OR 'acquired coagulopathies':ab,ti OR vka:ab,ti OR 'new oral anticoagulant':ab,ti OR 'newer oral anticoagulant':ab,ti OR noac OR 'non-vitamin k antagonist':ab,ti OR 'non-vitamin-k-antagonist':ab,ti OR 'non-vitamin k dependent antagonist':ab,ti OR doac OR 'direct oral anticoagulant':ab,ti)

AND
('antifibrinolytic agent'/exp OR 'antifibrinolytic agent' OR 'antifibrinolytic':ab,ti OR tranexamic:ab,ti OR 'aminocaproic acid':ab,ti OR cyclokapron:ab,ti OR cyklokapron:ab,ti OR eaca:ab,ti OR amicar:ab,ti OR txa:ab,ti)

The Cochrane Library (no restriction on publication data)

"oral surgery":ti,ab OR "oral surgical procedures":ti,ab OR dental:ti,ab OR tooth:ti,ab OR "operative dentistry":ti,ab OR molar:ti,ab OR dentoalveolar:ti,ab OR orthognathic:ti,ab OR periodontal:ti,ab
AND
anticoagulants:ti,ab OR anticoagulant:ti,ab OR anticoagulation:ti,ab OR anticoagulated:ti,ab OR "vitamin k antagonist":ti,ab OR "anti-vitamin k":ti,ab OR "antivitamin k":ti,ab OR "anti vitamin k":ti,ab OR "acquired disorder of coagulation":ti,ab OR "acquired coagulation disorder":ti,ab OR "acquired coagulopathy":ti,ab OR "acquired coagulopathies":ti,ab OR VKA:ti,ab OR warfarin:ti,ab OR phenprocoumon:ti,ab OR acenocoumarol:ti,ab OR coumadin:ti,ab OR coumadins:ti,ab OR coumarin:ti,ab OR coumarins:ti,ab OR "new oral anticoagulant":ti,ab OR "newer oral anticoagulant":ti,ab OR NOAC:ti,ab OR "non-vitamin k antagonist":ti,ab OR "non-vitamin-k-antagonist":ti,ab OR "non-vitamin k dependent antagonist":ti,ab OR DOAC:ti,ab OR "direct oral anticoagulant":ti,ab
AND
antifibrinolytic:ti,ab OR tranexamic:ti,ab OR cyclokapron:ti,ab OR cyklokapron:ti,ab OR eaca:ti,ab OR "aminocaproic acid":ti,ab OR amicar:ti,ab OR TXA:ti,ab

ClinicalTrials.gov (no restriction on publication data)

("oral surgery" OR dental OR tooth OR periodontal) AND (anticoagulant OR "vitamin k antagonist" OR VKA OR NOAC OR DOAC OR "direct oral anticoagulant") AND (antifibrinolytic OR tranexamic OR cyclokapron OR eaca OR "aminocaproic acid" OR TXA)

International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) (no restriction on publication data)

(oral surgery OR oral surgical procedures OR dental OR tooth OR operative dentistry OR molar OR dentoalveolar OR orthognathic OR periodontal)
AND
(anticoagulants OR anticoagulant OR anticoagulation OR anticoagulated OR vitamin k antagonist OR anti-vitamin k OR antivitamin k OR anti vitamin k OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR coumadin OR coumadins OR coumarin OR coumarins OR new oral anticoagulant OR newer oral anticoagulant OR NOAC OR non-vitamin k antagonist OR non-vitamin-k-antagonist OR non-vitamin k dependent antagonist OR DOAC OR direct oral anticoagulant)
AND
(antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR aminocaproic acid OR amicar OR TXA)

CINAHL database of nursing and allied health services (no restriction on publication data)

TI (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA) OR AB (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA)
AND
TI (anticoagulants OR anticoagulant OR anticoagulation OR anticoagulated OR "vitamin k antagonist" OR "anti-vitamin k" OR "antivitamin k" OR "anti vitamin k" OR "acquired disorder of coagulation" OR "acquired coagulation disorder" OR "acquired coagulopathy" OR "acquired coagulopathies" OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR coumadin OR coumadins OR coumarin OR coumarins OR "new oral anticoagulant" OR "newer oral anticoagulant" OR NOAC OR "non-vitamin k antagonist" OR "non-vitamin-k-antagonist" OR "non-vitamin k dependent antagonist" OR DOAC OR "direct oral anticoagulant") OR AB (anticoagulants OR anticoagulant OR anticoagulation OR anticoagulated OR "vitamin k antagonist" OR "anti-vitamin k" OR "antivitamin k" OR "anti vitamin k" OR "acquired disorder of coagulation" OR "acquired coagulation disorder" OR "acquired coagulopathy" OR "acquired coagulopathies" OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR coumadin OR coumadins OR coumarin OR coumarins OR "new oral anticoagulant" OR "newer oral anticoagulant" OR NOAC OR "non-vitamin k antagonist" OR "non-vitamin-k-antagonist" OR "non-vitamin k dependent antagonist" OR DOAC OR "direct oral anticoagulant")

AND
TI (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA) OR AB (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA)

Open access Proquest dissertation database (no restriction on publication data)

"(oral surgery OR oral surgical procedures OR dental OR tooth OR operative dentistry OR molar OR dentoalveolar OR orthognathic OR periodontal) AND ((anticoagulants OR anticoagulant OR anticoagulation OR anticoagulated OR vitamin k antagonist OR anti-vitamin k OR antivitamin k OR anti vitamin k OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR coumadin OR coumadins OR coumarin OR coumarins OR new oral anticoagulant OR newer oral anticoagulant OR NOAC OR non-vitamin k antagonist OR non-vitamin-k-antagonist OR non-vitamin k dependent antagonist OR DOAC OR direct oral anticoagulant) AND ((antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR aminocaproic acid OR amicar OR TXA)"

American College of Clinical Pharmacy (ACCP) (no restriction on publication data)

("oral surgery" OR dental OR tooth OR molar OR dentoalveolar OR orthognathic OR periodontal) AND (anticoagulant OR anticoagulation OR "vitamin k antagonist" OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR Coumadin OR coumarin OR "new oral anticoagulant" OR NOAC OR "non-vitamin k antagonist" OR "non-vitamin-k-antagonist" OR "non-vitamin k dependent antagonist" OR DOAC OR "direct oral anticoagulant") AND (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA)

Abstract books of the annual scientific meeting of the International Society for Thrombosis and Haemostasis (no restriction on publication data)

("oral surgery" OR dental) AND (anticoagulant OR VKA) AND (antifibrinolytic OR tranexamic OR eaca)

European Haematology Association conference (no restriction on publication data)

(oral surgery OR dental OR tooth OR molar OR dentoalveolar OR orthognathic OR periodontal) AND (anticoagulant OR anticoagulation OR vitamin k antagonist OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR Coumadin OR coumarin OR new oral anticoagulant OR NOAC OR non-vitamin k antagonist OR DOAC OR direct oral anticoagulant) AND (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR aminocaproic acid OR amicar OR TXA)

American Society of Hematology conference (no restriction on publication data)

(oral surgery OR dental OR tooth OR molar OR dentoalveolar OR orthognathic OR periodontal) AND (anticoagulant OR anticoagulation OR vitamin k antagonist OR VKA OR warfarin OR phenprocoumon OR acenocoumarol OR Coumadin OR coumarin OR new oral anticoagulant OR NOAC OR non-vitamin k antagonist OR DOAC OR direct oral anticoagulant) AND (antifibrinolytic OR tranexamic OR cyclokapron OR cyklokapron OR eaca OR aminocaproic acid OR amicar OR TXA)

British Society for Haematology Annual Scientific Meeting (no restriction on publication data)

("oral surgery" OR dental OR tooth OR periodontal) AND (anticoagulant OR anticoagulation OR "vitamin k antagonist" OR VKA OR warfarin OR coumarin OR new oral anticoagulant OR NOAC OR non-vitamin k antagonist OR DOAC OR direct oral anticoagulant) AND (antifibrinolytic OR tranexamic OR cyclokapron OR eaca OR "aminocaproic acid" OR amicar OR TXA)

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KPM van Galen: guarantor of the review, conceiving, designing, coordinating and writing of the review, data collection, extraction and critical appraisal. Screening of search results and of retrieved papers against eligibility criteria. Data analysis and interpretation.

ET Engelen: designing search strategies en undertaking searches. Screening of search results and of retrieved papers against eligibility criteria. Data collection, extraction and critical appraisal.

RJJ van Es: interpretation of data, providing a clinical perspective and general advice on the review.

EP Mauser-Bunschoten: interpretation of data, providing a methodological, clinical, consumer and policy perspective.

REG Schutgens: supervising of the review, securing funding. Verifying the data extraction of trials identified for inclusion.

DECLARATIONS OF INTEREST

There are no potential conflicts of interest for any of the authors. None of the authors have been involved in any of the included trials potentially eligible for inclusion in the review.

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