Title

Safety of anticoagulation interruption in patients undergoing surgery: a systematic review and meta-analysis of randomised controlled trials and non-randomised studies.

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1. INTRODUCTION

1.1 Background and rationale

The management of patients taking long-term anticoagulation during the perioperative period remains a controversial issue. For clinicians, the main problem lies in balancing the risk of thromboembolic complications – which is inherent to temporary anticoagulation interruption – with the risk of perioperative bleeding associated to ongoing anticoagulation. To mitigate the risk of haemorrhage, bridging strategies based on short-acting or reversible anticoagulants (such as low-molecular-weight heparin or unfractionated heparin) have been proposed but systematic use has been inconsistent. Efforts to develop standardised protocols have been hampered by the fact that risk assessment in anticoagulated patients is a complex process that relies on multiple aspects, such as the indication for anticoagulation, patient specific comorbidities, concomitant medications (such as antiplatelet therapy), or the type of surgery.[1] The arrival of novel oral anticoagulants (NOAC) on the market has further compounded the issue, raising new challenges (such as the lack of reversibility of Xa-antagonists) for managing these patients in the perioperative period.[2]

Several factors account for the lack of consensus regarding peri-procedural anticoagulation strategies: to date, evidence has been mostly driven by observational studies of varying quality, comparing multiple strategies in diverse study groups, which resulted in conflicting results.[3-7] Additionally, in most previously published meta-analyses, data were combined despite high heterogeneity in study designs or in patient populations (for instance, thromboembolic risk differed between experimental and control groups), thereby limiting results interpretation.[8-13] Finally, a number of recently published studies have not been included in these previous reports.[14-17]

Therefore, the aim of this systematic review is to evaluate the safety of interrupting anticoagulation during the perioperative phase compared to continuing oral anticoagulation or administrating bridging therapy in patients requiring long-term oral anticoagulation. Since adverse events and mortality rates are likely to vary according to patient characteristics and surgical settings, evidence will be examined using a *context-specific approach*, as described elsewhere.[18] The effect of anticoagulation protocols diversity will also be explored, since different drugs or administration schemes may result in a varying degree of efficacy.

1.2 Objectives

The primary objective is to identify potential harmful effects of interrupting anticoagulation during the perioperative phase, in particular arterial/systemic or venous thromboembolic events. The rate of adverse events and mortality will be assessed across subsets of patients having a similar risk of developing complications, either because of their own individual characteristics (age, concomitant medication, comorbidities, indication for anticoagulation, thromboembolic risk scores) or because of the clinical setting (major versus minor surgery).

The following aspects will be considered as secondary objectives:
> To investigate if oral anticoagulation continuation or heparin bridging results in an increased risk of perioperative bleeding;
> To confirm the efficacy of oral anticoagulation continuation or heparin bridging in reducing perioperative thromboembolic events and mortality;
> To explore the effect of different types of anticoagulation protocols through subgroup analyses (oral anticoagulation continuation versus heparin bridging, type of anticoagulant drug, administration schema).

2. METHODS

We will follow the PRISMA guidelines for the reporting of systematic reviews[19] and specific recommendations for the reporting of meta-analyses including observational studies.[20,21]

2.1 Eligibility criteria

2.1.1 Type of studies

As we expect the available evidence to consist mostly of non-randomised studies, both randomised controlled trials (RCTs) and observational studies will be considered (Table 1).

For RCTs, only fully published reports comparing anticoagulation interruption *versus* any type of continuation (oral or heparin bridging) will be considered. If data are reported in several reports (duplicates), the first published article will be considered the main article.[22] The same rule will be applied to data reported in follow-up studies or in ancillary studies of larger RCTs.

Systematic reviews of non-randomised designs are methodologically challenging, since these studies are known to be at higher risk of bias and confounding.[20,21] Thus, only observational studies deemed to have a moderate risk of bias will be considered, i.e. studies with the following design features:

> Two or more groups receiving different interventions, studied over the same time period, where outcomes were measured in both groups and at the same time-point.

> Group allocation using inadequate randomisation methods (quasi-randomised trials) or based on a system of rules or a decisional algorithm defined by the researchers. Studies where group allocation occurred in a non-contemporary fashion, or where allocation was based on treatment decisions, on patient preferences, on differences in locations/areas or on the basis of the outcome will be excluded.

> Prospective identification of participants, assessment of baseline characteristics, allocation to treatment and assessment of outcomes.

> Strictly comparable groups: control group similar to experimental group in all respects other than the intervention, adjustment for confounding (such as thromboembolic risk, for instance).

Table 1. Type of included studies

Design features	Description
Identification of participants:	Prospective
Assessment of baseline characteristics:	Prospective
Allocation to intervention:	Prospective
Randomisation methods:	Adequate
	Inadequate (quasi-randomised)
	Based on researchers decision
Comparison:	2 groups or more
Intervention:	Differs between groups
Outcome assessment:	Prospective
	In both groups
	Over the same time period
	At the same time-point

2.1.2 Type of participants and settings

We will consider studies performed in adult patients (≥18 years old) taking any type of oral anticoagulation (standard or novel therapies) for the prevention of thromboembolic disease and admitted to a medical

facility for a surgical procedure. Trials performed in an acute care setting (emergency or intensive care unit) will be considered only if patients undergo subsequent surgical procedures. Data from animal or paediatric studies will be excluded.

2.1.3 Type of intervention

We will search for studies comparing anticoagulation interruption *versus* any type of continuation (oral or heparin bridging). All anticoagulant drugs will be considered (standard or novel therapies, unfractionated or low-molecular-weight heparin bridging). No restriction regarding doses, administration schema or duration will be applied.

2.2 Outcomes measures

The primary objective is to identify potential harmful effects of interrupting anticoagulation during the perioperative phase, in particular arterial or venous thromboembolic events. Thus, we will search for studies reporting:

> Venous thromboembolic events: deep venous thrombosis or pulmonary embolism occurring during the hospital stay or within 30 days;

> Ischaemic/arterial thromboembolic events: myocardial infarction, stroke/transient ischaemic attack (TIA), mesenteric or peripheral ischaemia occurring during the hospital stay or within 30 days;

> Early mortality: in-hospital or 30-day mortality rates. In studies reporting both, only the longest time period will be considered.

The following endpoints will be considered as secondary outcomes:

> Haemorrhagic events (surgical bleeding, GI bleeding, intracerebral haemorrhage) occurring during the hospital stay or within 30 days;

> To fully capture bleeding events, the following clinical indicators will also be extracted: surgical blood loss (ml), fluid therapy (ml), perioperative haemoglobin/haematocrit values, need for allogeneic blood products (type and number of units per patient), and concomitant blood management measures (administration of antifibrinolytics or clotting factor concentrates).

2.3 Search methods for identification of studies

We will search for relevant reports in the Medline (Ovid), Embase and Central databases (see search strategy – Appendix 1). The following sources of grey literature will be screened: OpenSIGLE, NTIS, International Clinical Trials Registry Platform, ClinicalTrials.gov. Additional reports will be identified by hand searching bibliographies of retrieved articles. No language or date restriction will be applied. Potentially relevant articles published in foreign languages will be translated and eventually assessed for eligibility.

2.4 Data collection and extraction

Titles and abstracts of retrieved articles will be screened by two independent reviewers (FH, SK) and potentially relevant reports will be subsequently assessed for eligibility. Duplicate publications will be identified through comparison of reports for: shared author names; similar date/duration of the study; similar setting or intervention; identical number of participants or baseline data. Disagreements will be resolved through discussion between the two reviewers.

The following information will be retrieved:

> RCTs extraction form:

>> General information about the study: first author, year of publication, trial registry number, related articles, source;

>> Eligibility criteria: RCT, human, ≥18 years, perioperative care setting, taking oral anticoagulation, anticoagulation interruption *versus* continuation or heparin bridging;

>> Study characteristics: design, duration, surgical setting;

>> Patients characteristics: total number of participants, particular eligibility criteria, age, gender, chronic disease, laboratory values, other relevant medication (e.g. antiplatelet drugs), indication for anticoagulation, type of oral anticoagulation, thromboembolic risk scores;

>> Intervention characteristics: definition of experimental and control groups, number of participants in each group, description of the intervention (type of placebo, continued anticoagulation or heparin bridging, administration schema, compliance to intervention);

>> Outcome characteristics: definition of primary and secondary outcomes, units/limits used, how and when the outcomes were detected. Only pre-specified outcomes as outlined in 2.2 will be collected.

> Non-randomised studies extraction form:

>> General information about the study: first author, year of publication, related articles, source;

>> Study characteristics: design (as specified in 2.1.1), duration, surgical setting;

>> Eligibility criteria: human, ≥18 years, perioperative care setting, taking oral anticoagulation, anticoagulation interruption *versus* continuation or heparin bridging, moderate risk of bias design;

>> Patients characteristics: total number of participants, particular eligibility criteria, age, gender, chronic disease, laboratory values, other relevant medication (e.g. antiplatelet drugs), indication for anticoagulation, type of oral anticoagulation, thromboembolic risk scores;

>> Intervention characteristics: definition of experimental and control groups, number of participants in each group, description of the intervention (type of placebo, continued anticoagulation or heparin bridging, administration schema, compliance to intervention);

>> Outcome characteristics: definition of primary and secondary outcomes, units/limits used, how and when the outcomes were detected. Only pre-specified outcomes as outlined in 2.2 will be collected.

Data will be extracted from original reports by two independent reviewers (FH, SK) using 2 data extraction forms specifically designed for this review (Microsoft Excel spread sheet). Any queries will be resolved through discussion. If data are missing, unclear or incomplete in the original report, the authors will be contacted for further clarification. Data obtained from duplicate publications will be extracted and merged under a unique study identification name.

All data will be subsequently entered into the Cochrane Review Manager software (RevMan 5.2.3) by 2 independent reviewers (FH, SK).

2.5 Quality assessment

For RCTs, quality of data reporting will be assessed using the Cochrane "Risk of bias" tool, which evaluates: method of randomisation, concealment of treatment allocation, blinding of participants and personnel, blinding of outcome assessor, risk of incomplete outcome data (reporting of dropouts) and risk of selective reporting *(Cochrane Handbook for Systematic Reviews of Interventions* – version 5.1.0, accessed online June 2016 at http://www.cochrane.org/handbook). Other sources of bias not included in this tool (i.e. ethics approval and informed consent; funding; potential conflict of interest; statistical issues) will also be assessed. The effects of detection and attrition bias will be specifically explored, since this may affect studies evaluating adverse events (AE).[23]

For non-randomised studies, a modified version of the Cochrane "Risk of bias" tool will be used to assess quality of data reporting, as recommended elsewhere.[20] The evaluation of selection bias will be based on groups comparability, method of group allocation and methods used to adjust for group imbalances (restriction, adjusted/stratified analysis). The risk of bias due to confounding will be thoroughly assessed. Other sources of bias will be evaluated using the following criteria: blinding of participants and personnel, quality/fidelity of the provided intervention (performance bias); blinding of outcome assessors, systematic outcome assessment (detection bias); completeness of sample, follow-up and data (attrition bias); selective

outcome reporting, publication bias (reporting bias).

2.6 Synthesis of results

For RCTs, dichotomous outcomes will be reported as risk ratios with 95% confidence intervals (CI), while continuous data will be expressed as weighted mean differences with 95% CI. Methods used for data handling (data combination for studies using more than 2 groups, data transformation in trials using different outcome scales) will be thoroughly described.

For non-randomised studies both adjusted and unadjusted effect estimates will be extracted but data synthesis will be primarily based on estimates adjusting for the maximum number of covariates or important confounders. Dichotomous outcomes will be reported as risk ratios with 95% confidence intervals (CI), while continuous data will be expressed as weighted mean differences with 95% CI.

2.7 Methods of analysis

Since adverse events and mortality rates are likely to vary according to patient characteristics and surgical settings, we will use a *context-specific* approach and stratify the analysis by: (1) patient-specific risk of developing complications (according to age, comorbidities, concomitant medication, indication for anticoagulation, thromboembolic risk scores); (2) setting-related risk of complications (type of surgery). Studies conducted in similar populations and settings will be regrouped into *risk strata*.

For RCTs, meta-analyses will be performed only if data are obtained from at least 2 studies.

For non-randomised studies, only studies with similar design features will be combined. We will use a particular method accounting for a high risk of confounding (generic inverse-variance method).

If data combination is deemed inappropriate, data will be summarised using a qualitative assessment.

To assess if our context-specific approach is sensible, we will also conduct a non-stratified analysis (i.e. data pooling without controlling for clinical diversity) and perform a test of interaction using the Cochran's Q and Higgins's I^2. We will consider that different population parameters were represented within each risk stratum when the Cochran's Q p-value is <0.05 or when I^2 is >50%.[24,25]

Statistical heterogeneity will be assessed by visual inspection of forest plots and by using the chi^2 test and the I^2 statistic. If data are heterogeneous (P <0.1, I^2>50%) we will search for methodological sources of heterogeneity.[24] We will use a fixed-effect model, unless overt clinical or residual statistical heterogeneity are present.[25,26]

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Appendix 1 – Search Strategy

1. Medline/Ovid

1. exp emergency treatment/ or *critical care/ or *intensive care/ or exp perioperative care/ or *preoperative care/ or *surgical procedures, operative/

2. (intensive care or ICU or critical care or acute care).tw.

3. (intraoperative or perioperative or postoperative).tw.

4. 1 or 2 or 3

5. exp Heparin/

6. exp Anticoagulants/ or exp Coumarins/

7. (heparin or anticoagulant* or coumarin* or warfarin or vitamin K or antivitamin K).tw.

8. 5 or 6 or 7

9. (bridging or continuation or cessation or interruption or stop or disruption or arrest or suspension).tw

10. 4 and 8 and 9

11. exp clinical trials as topic/ or intervention studies/

12. Random Allocation/

13. random*.tw.

14. placebo.tw.

15. randomi#ed controlled trial*.pt.

16. trial.tw.

17. groups.tw.

18. 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp animals/ not humans.sh.

20. 18 not 19

21. 10 and 20

2. Embase

1. 'perioperative period'/de OR 'preoperative period'/exp OR perioperative:ab,ti OR preoperative:ab,ti OR surg*:ab,ti OR operat*:ab,ti

2. 'heparin'/exp OR 'low molecular weight heparin'/exp OR 'antivitamin k'/exp OR 'coumarin anticoagulant'/exp OR heparin:ab,ti OR anticoagulant*:ab,ti OR coumarin*:ab,ti OR warfarin:ab,ti OR 'antivitamin k':ab,ti

3. 'bridging' OR 'continuation' OR 'cessation' OR 'interruption' OR 'stop' OR 'disruption' OR 'arrest' OR 'suspension':ab,ti

4. 'clinical trial (topic)'/exp OR 'clinical trial'/exp OR random*:ab,ti OR control*:ab,ti OR placebo:ab,ti OR group*:ab,ti OR trial:ab,ti

5. #1 AND #2 AND #3 AND #4

3. Cochrane

#1 MeSH descriptor: [Perioperative Care] explode all trees
#2 MeSH descriptor: [Perioperative Period] explode all trees
#3 MeSH descriptor: [Specialties, Surgical] explode all trees
#4 perioperative:ab,ti or preoperative:ab,ti or surg*:ab,ti or intensive care:ab,ti
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Heparin] explode all trees
#7 MeSH descriptor: [Coumarins] explode all trees
#8 MeSH descriptor: [Anticoagulants] explode all trees
#9 heparin:ab,ti or anticoagulant*:ab,ti or coumarin*:ab,ti or warfarin:ab,ti or 'antivitamin k':ab,ti
#10 #6 or #7 or #8 or #9
#11 #5 and #10
#12 'bridging' or 'continuation' or 'cessation' or 'interruption' or 'stop' or 'disruption' or 'arrest' or 'suspension':ab,ti
#13 #11 and #12