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Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)

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Abstract

Introduction: Bleeding during cardiac surgery is associated with increased morbidity and mortality. Tranexamic acid is an antifibrinolytic with proven efficacy in major surgeries. Current clinical practice guidelines recommend intraoperative use in cardiac procedures. However, several complications have been reported with tranexamic acid including seizures. intended to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery.

Methods/design: We will search MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry for eligible randomized controlled trials investigating the peri-operative use of topical and/or intravenous tranexamic acid as a stand-alone antifibrinolytic agent compared to placebo in patients undergoing open cardiac surgery. We categorized outcomes as patient critical or patient important. selected patient-critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein thrombosis, and seizures. Those outcomes, we perceived as clinical experts to be most patient valued and patients were not involved in outcomes selection process.

We will not apply publication date, language, journal, or methodological quality restrictions. Two reviewers will independently screen and identify eligible studies using predefined eligibility criteria and then review full reports of all potentially relevant citations. A third reviewer will resolve disagreements if consensus cannot be achieved.

We will present the results as relative risk (RR) with 95% confidence intervals for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) for continuous outcomes with 95% confidence intervals. We will assess the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: The aim of this systematic review is to summarize the updated evidence on the efficacy and safety of tranexamic acid in cardiac surgery.

Systematic review registration: Protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 26 October 2018 (registration number CRD42018105904).

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Keywords: Tranexamic acid, Cardiac surgery, Systematic review, Meta-analysis, Mortality,

Bleeding, Seizure.

Article Summary:

Our systematic review and meta-analysis are intended to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery. We will examine the effect of the type of surgery, patient population and dosing strategies.

Strengths and Limitations of this protocol include:

- A comprehensive search strategy of published and unpublished literature
- Application of grade methodology to assess certainty of the estimates of effect
- Limitations relate to the anticipated heterogeneity of the included studies including dosing strategy, timing, type of surgery and preoperative antiplatelets therapy.

Background

Description of the condition

15 million units of red blood cells transfused in surgical patients in the united states annually, Cardiac surgical procedures utilize as much as 10% to 15% [1]. Peri-operative bleeding is a common complication and is associated with the need for transfusion and re-operation [2,3]. These factors impact negatively on postoperative morbidity, mortality, and costs [4]. Coagulopathy, a contributor to excessive bleeding, is linked to the use of cardiopulmonary bypass, which leads to the activation of the intrinsic and extrinsic coagulation pathway, platelet dysfunction, and systemic inflammatory response [5,6,7]. As such, measures to prevent perioperative coagulopathy are recommended [8]. To this end, antifibrinolytic agents are used to prevent the breakdown of blood clots by plasmin.

Tranexamic acid is an antifibrinolytic agent that has be shown to reduce bleeding in major surgeries and trauma patients [9-10]. As a result, current clinical practice guidelines recommend its use in many perioperative settings, including cardiac surgery [11].

Description of the Intervention

Tranexamic acid acts by reversibly blocking the lysine binding sites of plasminogen, thus preventing plasmin activation and, as a result, the lysis of polymerized fibrin [12]. Tranexamic acid is frequently utilized to enhance hemostasis, particularly when fibrinolysis contributes to hemorrhage. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated hemorrhage, and to prevent perioperative bleeding associated with orthopedic and cardiac surgery [13-16]. Importantly, the use of tranexamic acid is not without adverse effects. Tranexamic acid has been associated with seizures [17,18], as well as increased thromboembolic events, graft thrombosis, stroke, and mesenteric ischemia [18-21]. These complications lead to increased mortality and morbidity, in addition to increased intensive care unit (ICU) and hospital lengths of stay (LOS) [22]. Moreover, both the route and quantity for administration of tranexamic acid has varied across cardiac surgery trials [23,24]. Tranexamic acid can be administered orally, topically, and intravenously. Topical and intravenous administration are most common in perioperative cardiac surgeries.

How does the intervention work?

Fibrinolysis is the mechanism of clot breakdown and involves a cascade of interactions between zymogens and enzymes that act in concert with clot formation to maintain blood flow [25]. During extracorporeal circulation, such as cardiopulmonary bypass (CPB) used in cardiac surgery, multiplex changes in hemostasis arise that include accelerated thrombin generation, platelet dysfunction, and enhanced fibrinolysis [26]. Tranexamic acid inhibits fibrinolysis, a putative mechanism of bleeding after cardiopulmonary bypass, by forming a reversible complex with plasminogen [27].

Why it is important to do this review

Currently, no definitive and up-to-date meta-analysis summarizes the efficacy and potential for harm of tranexamic acid in cardiac surgery. Two previous meta-analyses have been conducted, but they did not include recent large randomized controlled trials (RCTs). Furthermore, one of these reviews grouped tranexamic acid with aprotinin and aminocaproic acid [28] while the other only studied the effect in patients undergoing CABG without the use of cardiopulmonary bypass [29].

Objectives

We plan to conduct a systematic review and meta-analysis of RCTs to investigate the use of tranexamic acid in adult patients underwent cardiac surgery.

Methods/design

Types of studies

We will only include RCTs which studied tranexamic acid in adults who underwent open cardiac surgery.. We will impose no language or methodological quality restrictions.

Types of participants

The population of interest is adult patients (18 years of age or older) who underwent open cardiac surgery including but not limited to CABG (on- or off-pump and midline sternotomy or thoracotomy), valve surgery, or ascending aorta and arch surgery including combined surgeries. We will exclude studies investigating transcatheter valvular procedures.

Types of interventions and comparators

The intervention of interest is administration of tranexamic acid in the perioperative period (defined as between 24 hours pre-operatively and up to 24 hours post-operatively). We will include studies that examined the intravenous and topical mode of delivery of tranexamic acid and will include all dosing strategies. We will exclude studies that did not use tranexamic acid as a stand-alone agent (i.e. in combination with another antifibrinolytic). The comparator or control group must include only patients who did not receive antifibrinolytic agents (either usual care or placebo).

Types of outcome measures

We will focus on outcomes we perceive as clinical experts to be most patient-important in order to assess the efficacy and safety of tranexamic acid. We categorized outcomes from a patient-perspective as either critical or important. The selected critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein

thrombosis, and seizures. The important outcomes are: major bleeding (as defined by individual study authors), transfusion of other blood products (fresh frozen plasma and platelets), ICU length of stay, and hospital length of stay.

Search methods for identification of studies

We will search the following electronic databases: MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry from inception for eligible articles with no language restriction. Keyword search terms include tranexamic acid, antifibrinolytic, coronary artery bypass grafting, cardiac surgery, cardiac valve surgery, ascending aorta and arch surgery, lysine analogue, bleeding, re-sternotomy and CABG.

Searching other resources

Two reviewers will independently search for eligible articles. In addition, we will search for unpublished and ongoing trials on the WHO International Clinical Trials Registry (WHO ICTRP), metaRegister of Controlled Trials (mRCT), ClinicalTrials.gov, Conference Proceedings Citation Index-Science (CPCI-S) within the last 2 years. We will also search conference abstracts from the following societies published in the last two years: American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), American Society of Thoracic Surgeons (AATS), Canadian Cardiovascular Society (CCS), European Association for Cardio-Thoracic Surgery (EACTS), American Society of Anesthesiology (ASA), Society of Critical Care Medicine (SCCM), Canadian Critical Care Society (CCCS), and European Society of Intensive Care Medicine (ESICM).

Data collection and analysis

After identifying potentially relevant articles through the search process described above, reviewers working in pairs will independently screen all citations and references using specific pre-defined eligibility criteria. We will screen in two stages: first reviewing titles and abstracts, and second reviewing the full-text. Disagreements in screening will be resolved by discussion and consensus with the help of a third reviewer if needed.

Data Extraction and Management

Data extraction will be done independently and in duplicate using pre-designed data abstraction forms. Abstracted data will include the study title, first author, relevant demographic data, intervention and control, results for outcomes of interest, and information on the methodological quality for each study. A third reviewer will resolve discrepancies in data extraction between reviewers.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias of included studies using the Cochrane Collaboration tool for assessing risk of bias in RCTs [30]. We will assess risk of bias individually for each outcome. A third reviewer will be available to resolve any disagreements. For each study, we will include a description for all domains assessed, along with comments if necessary and a final judgment. The risk of bias of a trial will be categorized as follows: (1) low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) high risk of bias, where outcomes are likely to be significantly affected by bias, (3) unclear risk of bias, where the reported information is inadequate to properly assess bias.

Included trials will be assessed for adequate sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias. Sequence generation will be considered adequate if the study explicitly described an appropriate randomization procedure to generate an unpredictable sequence of allocation, including computerized randomization, use of random number tables, and coin tossing. Concealment of allocation will be considered adequate if specific methods to protect allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver, and/or researcher blinding. Blinding of outcome assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the a priori study protocol, if available. If the study protocol is not available, we will compare the outcomes listed in the "Methods/design" section with those reported in the manuscript.

Measures of treatment effect

When pooling of outcome data is appropriate, RevMan 5.3 software will be used to conduct meta-analyses. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a

random effects model; study weights will be measured using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) with 95% CIs for continuous outcomes.

We plan to perform random effects analysis for all outcomes of interest. If significant unexplained heterogeneity exists, or if there is an insufficient number of RCTs for meta-analysis, we will describe data qualitatively. The number needed to treat (NNT) with 95% CIs will be derived from pooled risk ratios and its 95% CIs utilizing assumed control risk (ACR) for each outcome similar to the approach recommended by the Cochrane collaboration; NNT = 1/[ACR x (1 – RR)] [31].

Dealing with missing data

If we encounter missing data, we will attempt contact the study authors for additional information. If we can not obtain additional data, we will analyze the available data and report the potential impact of missing data in the discussion.

Assessment of heterogeneity

We will assess for heterogeneity between studies using the chi-squared test for homogeneity, where $p < 0.10$ indicates substantial heterogeneity, and the I^2 statistic. We consider $I^2 > 50$ % to be significant heterogeneity, which will be further investigated with subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect.

Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than ten trials are included for an outcome. For continuous outcomes, the Egger test [30] will be used to detect funnel plot asymmetry. For dichotomous outcomes, we will use the arcsine test. All analyses will be performed using RevMan or Stata.

Subgroup analysis and investigation of heterogeneity

Potential and expected clinical sources of heterogeneity include different patient demographics, dosing strategies, route of administration, and type of cardiac surgery. To explore significant heterogeneity, if a sufficient number of trials are available, we will conduct the following pre-specified subgroup analyses (hypothesized direction of effect in parentheses):

- Off- versus on-pump cardiac surgery (tranexamic acid is more effective in on-pump surgery)
- Type of surgery (tranexamic acid is more effective in valvular heart surgery or aortic arch/ascending aorta surgery as compared to CABG)
- Combined procedures versus single procedure (tranexamic acid is more effective in combined procedures)
- Urgent versus elective surgery (tranexamic acid is more effective in urgent surgeries)
- Single dose versus multiple doses and/or continuous infusion (multiple doses or continuous infusion is more effective)
- Patients who received aspirin within 4 days of their procedure vs. no antiplatelets agents (tranexamic acid is more effective in those receiving antiplatelets)
- Patients receiving dual antiplatelets within 4 days of procedure (tranexamic acid is more effective in those receiving dual antiplatelets)
- High versus low risk for bias studies (tranexamic acid is more effective in high risk of bias studies).

We will use the Chi-squared test for each subgroup hypothesis ($p<0.10$ for significance). We will conduct meta-regression to assess the effect of tranexamic dose as a continuous independent variable on the outcomes using Stata hypothesizing that higher dose is more effective. If subgroups effects are credible, we will present the outcomes separately for each subgroup.

Sensitivity analysis

A priori sensitivity analysis will be performed, excluding studies only reported as abstracts. Post hoc sensitivity analysis will be performed if required.

Assessing the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence for each outcome [32]. The GRADE system classifies the quality of the aggregate body of evidence as high, moderate, low, or very low. The evidence will be evaluated using the following criteria: (1) study design and rigor of its execution (i.e. individual study risk of bias), (2) the

extent to which the evidence could be applied to patients of interest (i.e. directness), (3) the consistency of results, (4) the analysis of the results (i.e. precision), and (5) the likelihood of publication bias. The following three factors will increase the quality of evidence if present: (1) a strong or very strong association between an intervention and the observation of interest, (2) a highly statistically significant relationship between dose and effect, and (3) a plausible confounding variable that could explain a reduced effect or could explain an effect if one was not anticipated. We will summarize the overall quality of evidence for the intervention taking into consideration both desirable and adverse outcomes. We will include an evidence profile in the results showing the GRADE assessments and pooled analysis per outcome.

Patient and Public Involvement:

We categorized outcomes as we perceived it as clinical experts to be more patient valued into patient critical and patient important outcomes. but there were no patients involved in the process of selection.

DISCUSSION

Bleeding is one of the major complications of cardiac surgeries [5]. The inhibition of fibrinolysis inhibition using lysine analogues is a common approach used to reduce the intra and post-operative bleeding associated with cardiac surgery [33]. Tranexamic acid is the most common lysine analogue used in clinical use. Despite its benefits in the prevention of bleeding that has been repeatedly reported tranexamic acid has not been shown to reduce mortality. Tranexamic acid has existing safety concerns, including elevated risks of myocardial infarction, stroke, veno-thromboembolic disease and seizures [17-21]. Despite trial level data, the balance between bleeding prevention and the hypothetical side effects of tranexamic acid remains uncertain.

Our systematic review and meta-analysis are intended to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery. We will examine the effect of the type of surgery, patient population and dosing strategies. Strengths of this protocol include a comprehensive search strategy of published and unpublished literature and application of GRADE methodology to assess certainty of the estimates of effect. Limitations relate to the anticipated heterogeneity of the included studies.

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Conflict of interest: Authors have no conflict of interest to declare.

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Contributors TA, AA, BR,CA,EB conceived the idea for this systematic review. All authors developed the methodology for the systematic review. The manuscript was drafted by TA,AA,DX and BR and revised by all authors. TA,AA and DX will screen potential studies perform duplicate independent data abstraction, risk of bias assessment and GRADE assessment with help from other authors. BR will conduct the data synthesis. BR is the guarantor of the review.

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Abstract

Introduction: Bleeding during cardiac surgery is associated with increased morbidity and mortality. Tranexamic acid is an antifibrinolytic with proven efficacy in major surgeries. Current clinical practice guidelines recommend intraoperative use in cardiac procedures. However, several complications have been reported with tranexamic acid including seizures. This review intends to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery.

Methods/design: We will search MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry for eligible randomized controlled trials , the search dates for all databases will be from inception until January 1st 2019, investigating the peri-operative use of topical and/or intravenous tranexamic acid as a stand-alone antifibrinolytic agent compared to placebo in patients undergoing open cardiac surgery. We categorized outcomes as patient critical or patient important. selected patient-critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein thrombosis, and seizures. Those outcomes, we perceived as clinical experts to be most patient valued and patients were not involved in outcomes selection process.

We will not apply publication date, language, journal, or methodological quality restrictions. Two reviewers will independently screen and identify eligible studies using predefined eligibility criteria and then review full reports of all potentially relevant citations. A third reviewer will resolve disagreements if consensus cannot be achieved.

We will present the results as relative risk (RR) with 95% confidence intervals for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) for continuous outcomes with 95% confidence intervals. We will assess the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication

Systematic review registration: Protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 26 October 2018 (registration number CRD42018105904).

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Keywords: Tranexamic acid, Cardiac surgery, Systematic review, Meta-analysis, Mortality,

Bleeding, Seizure.

Article Summary:

Strengths and Limitations of this protocol include:

- A comprehensive search strategy of published and unpublished literature
- Application of grade methodology to assess certainty of the estimates of effect
- Limitations relate to the anticipated heterogeneity of the included studies including dosing strategy, timing, type of surgery and preoperative antiplatelets therapy.

Background

Description of the condition

Surgical patients in the United States receive 15 million units of red blood cell transfusions annually, cardiac surgical procedures utilize as much as 10% to 15% of this [1]. Peri-operative bleeding is a common complication and is associated with the need for transfusion and re-operation [2,3]. These factors impact negatively on postoperative morbidity, mortality, and costs [4]. Coagulopathy, a contributor to excessive bleeding, is linked to the use of cardiopulmonary bypass, which leads to the activation of the intrinsic and extrinsic coagulation pathway, platelet dysfunction, and systemic inflammatory response [5,6,7]. As such, measures to prevent perioperative coagulopathy are recommended [8]. To this end, antifibrinolytic agents are used to prevent the breakdown of blood clots by plasmin.

Tranexamic acid is an antifibrinolytic agent that has be shown to reduce bleeding in major surgeries and trauma patients [9-10]. As a result, current clinical practice guidelines recommend its use in many perioperative settings, including cardiac surgery [11].

Description of the Intervention

Tranexamic acid acts by reversibly blocking the lysine binding sites of plasminogen, thus preventing plasmin activation and, as a result, the lysis of polymerized fibrin [12]. Tranexamic acid is frequently

utilized to enhance hemostasis, particularly when fibrinolysis contributes to bleeding. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated bleeding, and to prevent perioperative bleeding associated with orthopedic and cardiac surgery [13-16]. Importantly, the use of tranexamic acid is not without adverse effects. Tranexamic acid has been associated with seizures [17,18], as well as concerns of possible increased thromboembolic events, including stroke which to-date have not been demonstrated in randomized controlled trials [19-20]. Stroke after cardiac surgery might lead to increased mortality and morbidity, in addition to increased intensive care unit (ICU) and hospital lengths of stay (LOS) [21-22]. Moreover, both the route and quantity for administration of tranexamic acid has varied across cardiac surgery trials [23,24]. Tranexamic acid can be administered orally, topically, and intravenously. Topical and intravenous administration are most common in perioperative cardiac surgeries.

How does the intervention work?

Fibrinolysis is the mechanism of clot breakdown and involves a cascade of interactions between zymogens and enzymes that act in concert with clot formation to maintain blood flow [25]. During extracorporeal circulation, such as cardiopulmonary bypass (CPB) used in cardiac surgery, multiplex changes in hemostasis arise that include accelerated thrombin generation, platelet dysfunction, and enhanced fibrinolysis [26]. Tranexamic acid inhibits fibrinolysis, a putative mechanism of bleeding after cardiopulmonary bypass, by forming a reversible complex with plasminogen [27].

Why it is important to do this review

Currently, no definitive and up-to-date meta-analysis summarizes the efficacy and potential for harm of tranexamic acid in cardiac surgery. Several meta-analyses have been conducted, but they did not include recent large randomized controlled trials (RCTs) [20] or comprehensively looked at both efficacy and harm. Furthermore, one of these reviews grouped tranexamic acid with aprotinin and aminocaproic acid [28] while the most recent meta-analysis studied the effect in patients undergoing CABG without the use of cardiopulmonary bypass [29].

Objectives

We plan to conduct a systematic review and meta-analysis of RCTs to investigate the use of tranexamic acid in adult patients underwent cardiac surgery.

Methods/design

Types of studies

We will only include RCTs which studied tranexamic acid in adults who underwent open cardiac surgery.. We will impose no language or methodological quality restrictions.

Types of participants

The population of interest is adult patients (18 years of age or older) who underwent open cardiac surgery including but not limited to CABG (on- or off-pump and midline sternotomy or thoracotomy), valve surgery, or ascending aorta and arch surgery including combined surgeries. We will exclude studies investigating transcatheter valvular procedures.

Types of interventions and comparators

The intervention of interest is administration of tranexamic acid in the perioperative period (defined as between 24 hours pre-operatively and up to 24 hours post-operatively). We will include studies that examined the intravenous and topical mode of delivery of tranexamic acid and will include all dosing strategies. We will exclude studies that did not use tranexamic acid as a stand-alone agent (i.e. in combination with another antifibrinolytic). The comparator or control group must include only patients who did not receive antifibrinolytic agents (either usual care or placebo).

Types of outcome measures

We will focus on outcomes we perceive as clinical experts to be most patient-important in order to assess the efficacy and safety of tranexamic acid. We categorized outcomes from a patient-perspective as either critical or important. The selected critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein

thrombosis, and seizures. The important outcomes are: bleeding (defined as chest tube output in milliliter within 24 hours post-operatively), transfusion of other blood products (fresh frozen plasma and platelets), ICU length of stay, and hospital length of stay. The time frame for all outcomes is during ICU stay unless otherwise mentioned.

Search methods for identification of studies

We will search the following electronic databases: MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry from inception for eligible articles with no language restriction. Keyword search terms include tranexamic acid, antifibrinolytic, coronary artery bypass grafting, cardiac surgery, cardiac valve surgery, ascending aorta and arch surgery, lysine analogue, bleeding, re-sternotomy and CABG; detailed search strategy (supplementary file). search dates for all databases will be from inception until January 1st, 2019. Although we plan to update the search just prior to submission to ensure it is as up to date as possible

Searching other resources

Two reviewers will independently search for eligible articles. In addition, we will search for unpublished and ongoing trials on the WHO International Clinical Trials Registry (WHO ICTRP), metaRegister of Controlled Trials (mRCT), ClinicalTrials.gov, Conference Proceedings Citation Index-Science (CPCI-S). We will also search conference abstracts from the following societies published in the last two years: American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), American Society of Thoracic Surgeons (AATS), Canadian Cardiovascular Society (CCS), European Association for Cardio-Thoracic Surgery (EACTS), American Society of Anesthesiology (ASA), Society of Critical Care Medicine (SCCM), Canadian Critical Care Society (CCCS), and European Society of Intensive Care Medicine (ESICM).

Data collection and analysis

After identifying potentially relevant articles through the search process described above, reviewers working in pairs will independently screen all citations and references using specific pre-defined eligibility criteria. We will screen in two stages: first reviewing titles and abstracts, and second reviewing the full-

text. Disagreements in screening will be resolved by discussion and consensus with the help of a third reviewer if needed.

Data Extraction and Management

Data extraction will be done independently and in duplicate using pre-designed data abstraction forms. Abstracted data will include the study title, first author, relevant demographic data, intervention and control, results for outcomes of interest, and information on the methodological quality for each study. A third reviewer will resolve discrepancies in data extraction between reviewers.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias of included studies using the Cochrane Collaboration tool for assessing risk of bias in RCTs [30]. We will assess risk of bias individually for each outcome. A third reviewer will be available to resolve any disagreements. For each study, we will include a description for all domains assessed, along with comments if necessary and a final judgment. The risk of bias of a trial will be categorized as follows: (1) low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) high risk of bias, where outcomes are likely to be significantly affected by bias, (3) unclear risk of bias, where the reported information is inadequate to properly assess bias.

Included trials will be assessed for adequate sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias. Sequence generation will be considered adequate if the study explicitly described an appropriate randomization procedure to generate an unpredictable sequence of allocation, including computerized randomization, use of random number tables, and coin tossing. Concealment of allocation will be considered adequate if specific methods to protect allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver, and/or researcher blinding. Blinding of outcome assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the a priori study protocol, if available. If the study protocol is not available, we will compare the outcomes listed in the "Methods/design" section with those reported in the manuscript.

Measures of treatment effect

When pooling of outcome data is appropriate, RevMan 5.3 software will be used to conduct meta-analyses. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random effects model; study weights will be measured using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) with 95% CIs for continuous outcomes.

We plan to perform random effects analysis for all outcomes of interest. If significant unexplained heterogeneity exists, or if there is an insufficient number of RCTs for meta-analysis, we will describe data qualitatively. The number needed to treat (NNT) with 95% CIs will be derived from pooled risk ratios and its 95% CIs utilizing assumed control risk (ACR) for each outcome similar to the approach recommended by the Cochrane collaboration; NNT = 1/[ACR x (1 – RR)] [31].

Dealing with missing data

If we encounter missing data, we will attempt contact the study authors for additional information. If we can not obtain additional data, we will analyze the available data and report the potential impact of missing data in the discussion.

Assessment of heterogeneity

We will assess for heterogeneity between studies using the chi-squared test for homogeneity, where $p < 0.10$ indicates substantial heterogeneity, and the I^2 statistic. We consider $I^2 > 50$ % to be significant heterogeneity, which will be further investigated with subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect.

Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than ten trials are included for an outcome. For continuous outcomes, the Egger test [30] will be used to detect funnel plot asymmetry. For

dichotomous outcomes, we will use the arcsine test. All analyses will be performed using RevMan or Stata.

Subgroup analysis and investigation of heterogeneity

Potential and expected clinical sources of heterogeneity include different patient demographics, dosing strategies, route of administration, and type of cardiac surgery. To explore significant heterogeneity, if a sufficient number of trials are available, we will conduct the following pre-specified subgroup analyses (hypothesized direction of effect in parentheses):

- Off- versus on-pump cardiac surgery (tranexamic acid is more effective in on-pump surgery)
- Type of surgery (tranexamic acid is more effective in valvular heart surgery or aortic arch/ascending aorta surgery as compared to CABG)
- Combined procedures versus single procedure (tranexamic acid is more effective in combined procedures)
- Urgent versus elective surgery (tranexamic acid is more effective in urgent surgeries)
- Single dose versus multiple doses and/or continuous infusion (multiple doses or continuous infusion is more effective)
- High versus low risk for bias studies (tranexamic acid is more effective in high risk of bias studies).

We will use the Chi-squared test for each subgroup hypothesis ($p<0.10$ for significance). We will conduct meta-regression to assess the effect of tranexamic dose as a continuous independent variable on the outcomes using Stata hypothesizing that higher dose is more effective. If subgroups effects are credible, we will present the outcomes separately for each subgroup.

Sensitivity analysis

A priori sensitivity analysis will be performed, excluding studies only reported as abstracts. Post hoc sensitivity analysis will be performed if required.

Assessing the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence for each outcome [32]. The GRADE system classifies the quality of the aggregate body of evidence as high, moderate, low, or very low. The evidence will be evaluated using

the following criteria: (1) study design and rigor of its execution (i.e. individual study risk of bias), (2) the extent to which the evidence could be applied to patients of interest (i.e. directness), (3) the consistency of results, (4) the analysis of the results (i.e. precision), and (5) the likelihood of publication bias. The following three factors will increase the quality of evidence if present: (1) a strong or very strong association between an intervention and the observation of interest, (2) a highly statistically significant relationship between dose and effect, and (3) a plausible confounding variable that could explain a reduced effect or could explain an effect if one was not anticipated. We will summarize the overall quality of evidence for the intervention taking into consideration both desirable and adverse outcomes. We will include an evidence profile in the results showing the GRADE assessments and pooled analysis per outcome.

Patient and Public Involvement:

We categorized outcomes as we perceived it as clinical experts to be more patient valued into patient critical and patient important outcomes. but there were no patients involved in the process of selection.

DISCUSSION

Bleeding is one of the major complications of cardiac surgeries [5]. The inhibition of fibrinolysis inhibition using lysine analogues is a common approach used to reduce the intra and post-operative bleeding associated with cardiac surgery [33]. Tranexamic acid is the most common lysine analogue used in clinical use. Despite its demonstrated benefits in the prevention of bleeding. Tranexamic acid has not been shown to reduce mortality in cardiac surgery .. Despite trial level data, the balance between bleeding prevention and the hypothetical side effects of tranexamic acid remains uncertain.

Our systematic review and meta-analysis are intended to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery. We will examine the effect of the type of surgery, patient population and dosing strategies. Strengths of this protocol include a comprehensive search strategy of published and unpublished literature and application of GRADE methodology to assess certainty of the estimates of effect. Limitations relate to the anticipated heterogeneity of the included studies.

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Conflict of interest: Authors have no conflict of interest to declare.

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Contributors TA, AA, BR, CA, EB conceived the idea for this systematic review. All authors (TA,AA,DX,SF,JS,EB,AF,TK,KK,RZ,RW,and BR) developed the methodology for the systematic review. The manuscript was drafted by TA,AA,DX and BR and revised by all authors. TA,AA and DX will screen potential studies perform duplicate independent data abstraction, risk of bias assessment and GRADE assessment with help from other authors. BR will conduct the data synthesis. BR is the guarantor of the review.

Ethics and dissemination: Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication

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Database: Embase <1974 to 2018 September 10> Search Strategy:

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1 exp antifibrinolytic agent/ (28330)
2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or antiplasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).mp. (13957)
3 exp aprotinin/ (11678)
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10 exp cardiovascular surgery/ (612911)
11 exp heart surgery/ (325152)
12 exp heart valve surgery/ (82677)
13 exp thorax surgery/ (524265)
14 exp coronary artery surgery/ (114219)
15 exp coronary artery bypass graft/ (67199)
16 exp coronary artery bypass surgery/ (15326)
17 exp thorax/su [Surgery] (1103)
18 exp coronary artery bypass/ (67199)
19 exp sternotomy/ (17164)
20 exp sternum/su [Surgery] (877)
21 exp heart valve/su [Surgery] (3320)
22 exp off pump coronary surgery/ (5258)
23 (exp heart/ or exp heart valve/ or exp heart disease/ or exp coronary artery disease/) and (su.fs. or surgery.mp. or surgeries.mp. or surgical.mp. or operate.mp. or operation.mp. or operations.mp. or bypass.mp. or stent*.mp. or graft*.mp. or repair.mp.) (493732)
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27 9 and 26 (6799)
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30 28 or 29 (1622208)
31 9 and 26 and 30 (1237)

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Title : Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)	Page 1
Update	1b	N/A	
Registration	2	PROSPERO registration number CRD42018105904	Pg 2
Authors:			
Contact	3a	Provided name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
Amendments	4	N/A	
Support:			
Sources	5a	The author(s) received no specific funding for this work	Pg 2,8
Sponsor	5b	N/A	
Role of sponsor or funder	5c	N/A	
INTRODUCTION			
Rationale	6	Rationale intended to summarize the evidence examining the efficacy and safety of TXA in cardiac surgery in abstract pg 2 and under why it is important to do this review pages 3 and 4	Pg2-4
Objectives	7	PICO question was explained under Methods/Design on page 4 under types of studies ,participants, intervention and comparator and outcome measures	Pg 4
METHODS			
Eligibility criteria	8	explained under Methods/Design on page 4 under types of studies, participants, intervention and comparator and outcome measures	Page 4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage under search methods and searching other resources	Pg.4-5
Search strategy	10	Uploaded separately as a supplementary document “EMBASE search strategy”	Supp1
Study records:			

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*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)

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Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)

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Abstract

Introduction: Bleeding during cardiac surgery is associated with increased morbidity and mortality. Tranexamic acid is an antifibrinolytic with proven efficacy in major surgeries. Current clinical practice guidelines recommend intraoperative use in cardiac procedures. However, several complications have been reported with tranexamic acid including seizures. This review intends to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery.

Methods/design: We will search MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry for eligible randomized controlled trials , the search dates for all databases will be from inception until January 1st 2019, investigating the peri-operative use of topical and/or intravenous tranexamic acid as a stand-alone antifibrinolytic agent compared to placebo in patients undergoing open cardiac surgery. We categorized outcomes as patient critical or patient important. selected patient-critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction, stroke, pulmonary embolism, bowel infarction, upper or lower limb deep vein thrombosis, and seizures. Those outcomes, we perceived as clinical experts to be most patient valued and patients were not involved in outcomes selection process.

We will not apply publication date, language, journal, or methodological quality restrictions. Two reviewers will independently screen and identify eligible studies using predefined eligibility criteria and then review full reports of all potentially relevant citations. A third reviewer will resolve disagreements if consensus cannot be achieved.

We will present the results as relative risk (RR) with 95% confidence intervals for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) for continuous outcomes with 95% confidence intervals. We will assess the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Ethics and dissemination: Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication

Systematic review registration: Protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 26 October 2018 (registration number CRD42018105904).

Funding statement: The author(s) received no specific funding for this work

Keywords: Tranexamic acid, Cardiac surgery, Systematic review, Meta-analysis, Mortality,

Bleeding, Seizure.

Article Summary:

Strengths and Limitations of this protocol include:

- A comprehensive search strategy of published and unpublished literature
- Application of grade methodology to assess certainty of the estimates of effect
- Limitations relate to the anticipated heterogeneity of the included studies including dosing strategy, timing, type of surgery and preoperative antiplatelets therapy.

Background

Description of the condition

Surgical patients in the United States receive 15 million units of red blood cell transfusions annually, cardiac surgical procedures utilize as much as 10% to 15% of this [1]. Peri-operative bleeding is a common complication and is associated with the need for transfusion and re-operation [2,3]. These factors impact negatively on postoperative morbidity, mortality, and costs [4]. Coagulopathy, a contributor to excessive bleeding, is linked to the use of cardiopulmonary bypass, which leads to the activation of the intrinsic and extrinsic coagulation pathway, platelet dysfunction, and systemic inflammatory response [5,6,7]. As such, measures to prevent perioperative coagulopathy are recommended [8]. To this end, antifibrinolytic agents are used to prevent the breakdown of blood clots by plasmin.

Tranexamic acid is an antifibrinolytic agent that has be shown to reduce bleeding in major surgeries and trauma patients [9-10]. As a result, current clinical practice guidelines recommend its use in many perioperative settings, including cardiac surgery [11].

Description of the Intervention

Tranexamic acid acts by reversibly blocking the lysine binding sites of plasminogen, thus preventing plasmin activation and, as a result, the lysis of polymerized fibrin [12]. Tranexamic acid is frequently

utilized to enhance hemostasis, particularly when fibrinolysis contributes to bleeding. In clinical practice, tranexamic acid has been used to treat menorrhagia, trauma-associated bleeding, and to prevent perioperative bleeding associated with orthopedic and cardiac surgery [13-16]. Importantly, the use of tranexamic acid is not without adverse effects. Tranexamic acid has been associated with seizures [17,18], as well as concerns of possible increased thromboembolic events, including stroke which to-date have not been demonstrated in randomized controlled trials [19-20]. Stroke after cardiac surgery might lead to increased mortality and morbidity, in addition to increased intensive care unit (ICU) and hospital lengths of stay (LOS) [21-22]. Moreover, both the route and quantity for administration of tranexamic acid has varied across cardiac surgery trials [23,24]. Tranexamic acid can be administered orally, topically, and intravenously. Topical and intravenous administration are most common in perioperative cardiac surgeries.

How does the intervention work?

Fibrinolysis is the mechanism of clot breakdown and involves a cascade of interactions between zymogens and enzymes that act in concert with clot formation to maintain blood flow [25]. During extracorporeal circulation, such as cardiopulmonary bypass (CPB) used in cardiac surgery, multiplex changes in hemostasis arise that include accelerated thrombin generation, platelet dysfunction, and enhanced fibrinolysis [26]. Tranexamic acid inhibits fibrinolysis, a putative mechanism of bleeding after cardiopulmonary bypass, by forming a reversible complex with plasminogen [27].

Why it is important to do this review

Currently, no definitive and up-to-date meta-analysis summarizes the efficacy and potential for harm of tranexamic acid in cardiac surgery. Several meta-analyses have been conducted, but they did not include recent large randomized controlled trials (RCTs) [20] or comprehensively looked at both efficacy and harm. Furthermore, one of these reviews grouped tranexamic acid with aprotinin and aminocaproic acid [28] while the most recent meta-analysis studied the effect in patients undergoing CABG without the use of cardiopulmonary bypass [29].

Objectives

We plan to conduct a systematic review and meta-analysis of RCTs to investigate the use of tranexamic acid in adult patients underwent cardiac surgery.

Methods/design

Types of studies

We will only include RCTs which studied tranexamic acid in adults who underwent open cardiac surgery.. We will impose no language or methodological quality restrictions.

Types of participants

The population of interest is adult patients (18 years of age or older) who underwent open cardiac surgery including but not limited to CABG (on- or off-pump and midline sternotomy or thoracotomy), valve surgery, or ascending aorta and arch surgery including combined surgeries. We will exclude studies investigating transcatheter valvular procedures.

Types of interventions and comparators

The intervention of interest is administration of tranexamic acid in the perioperative period (defined as between 24 hours pre-operatively and up to 24 hours post-operatively). We will include studies that examined the intravenous and topical mode of delivery of tranexamic acid and will include all dosing strategies. We will exclude studies that did not use tranexamic acid as a stand-alone agent (i.e. in combination with another antifibrinolytic). The comparator or control group must include only patients who did not receive antifibrinolytic agents (either usual care or placebo).

Types of outcome measures

We will focus on outcomes we perceive as clinical experts to be most patient-important in order to assess the efficacy and safety of tranexamic acid. We categorized outcomes from a patient-perspective as either critical or important. The selected critical outcomes are: mortality (ICU, hospital and 30-day endpoints), re-operation within 24 hours, post-operative bleeding requiring transfusion of packed red blood cells, myocardial infarction(MI), stroke, venous thrombo-embolism (VTE) within 3 months (that includes

pulmonary embolism (PE), upper or lower limb deep vein thrombosis (DVT)), bowel infarction and seizures. The important outcomes are: bleeding (defined as chest tube output in milliliter within 24 hours post-operatively), transfusion of other blood products (fresh frozen plasma and platelets), ICU length of stay, and hospital length of stay. For thromboembolic complications: MI, stroke, VTE and bowel infarction we will capture harm to the longest duration of follow-up available in the included studies up to 3 months following surgery. The time frame for all other outcomes is during ICU stay unless otherwise mentioned.

Search methods for identification of studies

We will search the following electronic databases: MEDLINE, EMBASE, PubMED, ACPJC, CINAHL, and the Cochrane trial registry from inception for eligible articles with no language restriction. Keyword search terms include tranexamic acid, antifibrinolytic, coronary artery bypass grafting, cardiac surgery, cardiac valve surgery, ascending aorta and arch surgery, lysine analogue, bleeding, re-sternotomy and CABG; detailed search strategy (supplementary file). search dates for all databases will be from inception until January 1st, 2019. Although we plan to update the search just prior to submission to ensure it is as up to date as possible

Searching other resources

Two reviewers will independently search for eligible articles. In addition, we will search for unpublished and ongoing trials on the WHO International Clinical Trials Registry (WHO ICTRP), metaRegister of Controlled Trials (mRCT), ClinicalTrials.gov, Conference Proceedings Citation Index-Science (CPCI-S). We will also search conference abstracts from the following societies published in the last two years: American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), American Society of Thoracic Surgeons (AATS), Canadian Cardiovascular Society (CCS), European Association for Cardio-Thoracic Surgery (EACTS), American Society of Anesthesiology (ASA), Society of Critical Care Medicine (SCCM), Canadian Critical Care Society (CCCS), and European Society of Intensive Care Medicine (ESICM).

Data collection and analysis

After identifying potentially relevant articles through the search process described above, reviewers working in pairs will independently screen all citations and references using specific pre-defined eligibility criteria. We will screen in two stages: first reviewing titles and abstracts, and second reviewing the full-text. Disagreements in screening will be resolved by discussion and consensus with the help of a third reviewer if needed.

Data Extraction and Management

Data extraction will be done independently and in duplicate using pre-designed data abstraction forms. Abstracted data will include the study title, first author, relevant demographic data, intervention and control, results for outcomes of interest, and information on the methodological quality for each study. A third reviewer will resolve discrepancies in data extraction between reviewers.

Assessment of risk of bias in included studies

Two reviewers will independently assess the risk of bias of included studies using the Cochrane Collaboration tool for assessing risk of bias in RCTs [30]. We will assess risk of bias individually for each outcome. A third reviewer will be available to resolve any disagreements. For each study, we will include a description for all domains assessed, along with comments if necessary and a final judgment. The risk of bias of a trial will be categorized as follows: (1) low risk of bias, where bias is not present or if present, unlikely to affect outcomes, (2) high risk of bias, where outcomes are likely to be significantly affected by bias, (3) unclear risk of bias, where the reported information is inadequate to properly assess bias.

Included trials will be assessed for adequate sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias. Sequence generation will be considered adequate if the study explicitly described an appropriate randomization procedure to generate an unpredictable sequence of allocation, including computerized randomization, use of random number tables, and coin tossing. Concealment of allocation will be considered adequate if specific methods to protect allocation were documented and implemented. Performance bias will be considered low if a study reported participant, caregiver, and/or researcher blinding. Blinding of outcome assessment will be considered adequate if outcome assessors and adjudicators were blinded. Within-study selective reporting of outcomes will be examined by reviewing the a priori study protocol, if available. If the study protocol is not

available, we will compare the outcomes listed in the "Methods/design" section with those reported in the manuscript.

Measures of treatment effect

When pooling of outcome data is appropriate, RevMan 5.3 software will be used to conduct meta-analyses. We will use the method of DerSimonian and Laird to pool effect sizes for each outcome under a random effects model; study weights will be measured using the inverse variance method. We will present the results as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and as mean difference (MD) or standardized mean difference (SMD) with 95% CIs for continuous outcomes.

We plan to perform random effects analysis for all outcomes of interest. If significant unexplained heterogeneity exists, or if there is an insufficient number of RCTs for meta-analysis, we will describe data qualitatively. The number needed to treat (NNT) with 95% CIs will be derived from pooled risk ratios and its 95% CIs utilizing assumed control risk (ACR) for each outcome similar to the approach recommended by the Cochrane collaboration; NNT = 1/[ACR x (1 – RR)] [31].

Dealing with missing data

If we encounter missing data, we will attempt contact the study authors for additional information. If we can not obtain additional data, we will analyze the available data and report the potential impact of missing data in the discussion.

Assessment of heterogeneity

We will assess for heterogeneity between studies using the chi-squared test for homogeneity, where $p < 0.10$ indicates substantial heterogeneity, and the I^2 statistic. We consider $I^2 > 50$ % to be significant heterogeneity, which will be further investigated with subgroup analyses to assess clinical and methodological sources of heterogeneity in intervention effect.

Assessment of reporting biases

We will look for potential publication bias using a funnel plot if more than ten trials are included for an outcome. For continuous outcomes, the Egger test [30] will be used to detect funnel plot asymmetry. For dichotomous outcomes, we will use the arcsine test. All analyses will be performed using RevMan or Stata.

Subgroup analysis and investigation of heterogeneity

Potential and expected clinical sources of heterogeneity include different patient demographics, dosing strategies, route of administration, and type of cardiac surgery. To explore significant heterogeneity, if a sufficient number of trials are available, we will conduct the following pre-specified subgroup analyses (hypothesized direction of effect in parentheses):

- Off- versus on-pump cardiac surgery (tranexamic acid is more effective in on-pump surgery)
- Type of surgery (tranexamic acid is more effective in valvular heart surgery or aortic arch/ascending aorta surgery as compared to CABG)
- Combined procedures versus single procedure (tranexamic acid is more effective in combined procedures)
- Urgent versus elective surgery (tranexamic acid is more effective in urgent surgeries)
- Single dose versus multiple doses and/or continuous infusion (multiple doses or continuous infusion is more effective)
- High versus low risk for bias studies (tranexamic acid is more effective in high risk of bias studies).

We will use the Chi-squared test for each subgroup hypothesis ($p<0.10$ for significance). We will conduct meta-regression to assess the effect of tranexamic dose as a continuous independent variable on the outcomes using Stata hypothesizing that higher dose is more effective. If subgroups effects are credible, we will present the outcomes separately for each subgroup.

Sensitivity analysis

A priori sensitivity analysis will be performed, excluding studies only reported as abstracts. Post hoc sensitivity analysis will be performed if required.

Assessing the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to assess the quality of evidence for each outcome [32]. The GRADE system classifies the quality of the aggregate body of evidence as high, moderate, low, or very low. The evidence will be evaluated using the following criteria: (1) study design and rigor of its execution (i.e. individual study risk of bias), (2) the extent to which the evidence could be applied to patients of interest (i.e. directness), (3) the consistency of results, (4) the analysis of the results (i.e. precision), and (5) the likelihood of publication bias. The following three factors will increase the quality of evidence if present: (1) a strong or very strong association between an intervention and the observation of interest, (2) a highly statistically significant relationship between dose and effect, and (3) a plausible confounding variable that could explain a reduced effect or could explain an effect if one was not anticipated. We will summarize the overall quality of evidence for the intervention taking into consideration both desirable and adverse outcomes. We will include an evidence profile in the results showing the GRADE assessments and pooled analysis per outcome.

Patient and Public Involvement:

We categorized outcomes as we perceived it as clinical experts to be more patient valued into patient critical and patient important outcomes. but there were no patients involved in the process of selection.

DISCUSSION

Bleeding is one of the major complications of cardiac surgeries [5]. The inhibition of fibrinolysis inhibition using lysine analogues is a common approach used to reduce the intra and post-operative bleeding associated with cardiac surgery [33]. Tranexamic acid is the most common lysine analogue used in clinical use. Despite its demonstrated benefits in the prevention of bleeding. Tranexamic acid has not been shown to reduce mortality in cardiac surgery .. Despite trial level data, the balance between bleeding prevention and the hypothetical side effects of tranexamic acid remains uncertain.

Our systematic review and meta-analysis are intended to summarize the evidence examining the efficacy and safety of tranexamic acid in patients undergoing cardiac surgery. We will examine the effect of the type of surgery, patient population and dosing strategies. Strengths of this protocol include a comprehensive search strategy of published and unpublished literature and application of GRADE methodology to assess certainty of the estimates of effect. Limitations relate to the anticipated heterogeneity of the included studies.

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Conflict of interest: Authors have no conflict of interest to declare.

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Contributors TA, AA, BR, CA, EB conceived the idea for this systematic review. All authors (TA,AA,DX,SF,JS,EB,AF,TK,KK,RZ,RW,and BR) developed the methodology for the systematic review. The manuscript was drafted by TA,AA,DX and BR and revised by all authors. TA,AA and DX will screen potential studies perform duplicate independent data abstraction, risk of bias assessment and GRADE assessment with help from other authors. BR will conduct the data synthesis. BR is the guarantor of the review.

Ethics and dissemination: Formal ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication

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Database: Embase <1974 to 2018 September 10> Search Strategy:

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1 exp antifibrinolytic agent/ (28330)
2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or antiplasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).mp. (13957)
3 exp aprotinin/ (11678)
4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).mp. (15442)
5 exp tranexamic acid/ (10966)
6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethylcyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).mp. (58514)
7 exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/ (5997)
8 (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).mp. (16163)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (95478)
10 exp cardiovascular surgery/ (612911)
11 exp heart surgery/ (325152)
12 exp heart valve surgery/ (82677)
13 exp thorax surgery/ (524265)
14 exp coronary artery surgery/ (114219)
15 exp coronary artery bypass graft/ (67199)
16 exp coronary artery bypass surgery/ (15326)
17 exp thorax/su [Surgery] (1103)
18 exp coronary artery bypass/ (67199)
19 exp sternotomy/ (17164)
20 exp sternum/su [Surgery] (877)
21 exp heart valve/su [Surgery] (3320)
22 exp off pump coronary surgery/ (5258)
23 (exp heart/ or exp heart valve/ or exp heart disease/ or exp coronary artery disease/) and (su.fs. or surgery.mp. or surgeries.mp. or surgical.mp. or operate.mp. or operation.mp. or operations.mp. or bypass.mp. or stent*.mp. or graft*.mp. or repair.mp.) (493732)
24 ((heart or cardiac or coronary or cardiothoracic or cardio-thoracic or thoracic or cardio-pulmonary or cardiopulmonary or aortic or mitral or arch or on pump or off pump) adj3 (surgery or surgeries or surgical or operate or operation or operations or bypass or stent* or graft*)).mp. (330250)
25 (coronary artery bypass or coronary artery surgery or coronary bypass graft surgery or coronary artery bypass graft or coronary bypass graft or coronary artery bypass graft* or coronary artery bypass graft* or coronary artery graft* or CABG).mp. (100527)
26 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (1056258)
27 9 and 26 (6799)
28 randomi?ed.ab,ti,kw. or randomized controlled trial.pt. or controlled clinical trial.pt. or placebo.ab,ti,kw. or clinical trials as topic.sh. or random*.ab,ti,kw. or trial.ti. (1500424)
29 (crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure).de. or ((((((random* or factorial* or crossover* or cross over* or placebo* or assign* or allocat* or volunteer* or singl*) adj1 blind*) or cross) adj1 over*) or doubl*) adj1 blind*).de,ab,ti. (639992)
30 28 or 29 (1622208)
31 9 and 26 and 30 (1237)

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page Number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Title : Tranexamic Acid in Cardiac Surgery: a systematic review and meta-analysis (protocol)	Page 1
Update	1b	N/A	
Registration	2	PROSPERO registration number CRD42018105904	Pg 2
Authors:			
Contact	3a	Provided name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8
Amendments	4	N/A	
Support:			
Sources	5a	The author(s) received no specific funding for this work	Pg 2,8
Sponsor	5b	N/A	
Role of sponsor or funder	5c	N/A	
INTRODUCTION			
Rationale	6	Rationale intended to summarize the evidence examining the efficacy and safety of TXA in cardiac surgery in abstract pg 2 and under why it is important to do this review pages 3 and 4	Pg2-4
Objectives	7	PICO question was explained under Methods/Design on page 4 under types of studies ,participants, intervention and comparator and outcome measures	Pg 4
METHODS			
Eligibility criteria	8	explained under Methods/Design on page 4 under types of studies, participants, intervention and comparator and outcome measures	Page 4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage under search methods and searching other resources	Pg.4-5
Search strategy	10	Uploaded separately as a supplementary document “EMBASE search strategy”	Supp1
Study records:			

Data management	11a	Described under data collection and analysis	Page 5
Selection process	11b	Under data collection and analysis	Page 5
Data collection process	11c	method of extracting data from reports was mentioned under data collection and analysis	Pg 5
Data items	12	General data items were described under data extraction and analysis	Page 5
Outcomes and prioritization	13	Described under type of outcome measures	Page 4
Risk of bias in individual studies	14	methods for assessing risk of bias of individual studies under assessment of risk of bias in included studies	Page 5-6
Data synthesis	15a	Explained under Measures of treatment effect pg6 and subgroup analysis and investigation of heterogeneity page 6-7	Page 6-7
	15b	explained under Measures of treatment effect	Page 6
	15c	Was explained under subgroup analysis and investigation of heterogeneity	Page 6
	15d	explained under Measures of treatment effect	Page 6
Meta-bias(es)	16	Under Assessment of risk of bias pg5, Assessment of reporting biases pg 6, assessing quality of evidence pg7	Page 5-7
Confidence in cumulative evidence	17	Under assessing quality of evidence	Page 7

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