BMJ Open

The Safety and Efficacy of Tranexamic Acid in Bleeding Paediatric Trauma Patients: A Systematic Review Protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012947
Article Type:	Protocol
Date Submitted by the Author:	06-Jun-2016
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Surgery, Emergency medicine
Keywords:	TRAUMA MANAGEMENT, Bleeding disorders & coagulopathies < HAEMATOLOGY, Paediatric orthopaedic & trauma surgery < PAEDIATRIC SURGERY

BMJ Open protocol manuscript: The Safety and Efficacy of Tranexamic Acid in Bleeding Paediatric Trauma Patients: A Systematic Review of the Literature.

Title: The Safety and Efficacy of Tranexamic Acid in Bleeding Paediatric Trauma Patients: A Systematic Review Protocol.

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Keywords: tranexamic acid, trauma, hemorrhage, children, antifibrinolytics

Word count: 1996

ABSTRACT

Introduction: Trauma is the leading cause of death among children aged 1-18. Studies indicate that better control of bleeding could potentially prevent 10-20% of trauma-related deaths. The antifibrinolytic agent tranexamic acid (TxA) has shown promise in hemorrhage control in adult trauma patients. However, information on the potential benefits of TxA in children remains sparse. This review proposes to evaluate the current uses, benefits and adverse effects of TxA in the bleeding paediatric trauma population.

Methods and analysis: A structured search of bibliographic databases (e.g. Medline, EMBASE, PubMed, CINAHL, Cochrane CENTRAL) has been undertaken to retrieve randomized controlled trials (RCTs) and cohort studies that describe the use of TxA in paediatric trauma patients. To ensure that all relevant data were captured, the search did not contain any restrictions on language or publication time. After deduplication, citations will be screened independently by two authors, and selected for inclusion based on pre-specified criteria. Data extraction and risk of bias assessment will be done independently and in duplicate. Meta-analytic methods will be employed wherever appropriate.

Ethics and dissemination: This study will not involve primary data collection, and formal ethical approval will therefore not be required. The findings of this study will be disseminated through a peer-reviewed publication and at relevant conference meetings.

PROSPERO registration number: CRD42016038023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first systematic review to evaluate the uses and efficacy of tranexamic acid (TxA) in paediatric trauma patients.
- This study has a great potential for translation as current protocols in pediatric trauma are extrapolated from adult studies or generated from small diverse pediatric studies.
- The aims and objectives of this study were set by relevant stakeholders including a paediatric surgeon, a paediatric anesthesiologist, a paediatric emergency physician, and two hematologists.
- We anticipate that there will be few trials specifically evaluating the use of TxA in pediatric trauma patients and the numbers of patients within studies are likely to be small. The data available may be heterogenous and not suitable for meta-analysis.

INTRODUCTION

Trauma is a substantial cause of morbidity and mortality in both developed and developing countries.[1-3] In 2013, 973 million people worldwide sustained injuries that required medical attention and 4.8 million of these died from their injuries.[4] Trauma represents the leading cause of death and potential years of life lost (PYYL) among children and youth under the age of 18 years.[5 6] In 2004 an estimated 950,000 children under the age of 18 died of an injury world-

wide.[6] In the United States in 2012, 6.8 million children 18 years of age and younger were treated for trauma-related disorders, resulting in a total medical expenditure of US$7.8 billion.[7]

Hemorrhage continues to be the major cause of trauma-related death. Studies indicate that better control of bleeding could prevent 10-20% of these deaths.[8] Vascular injury normally triggers coagulation, a complex proteolytic cascade that culminates in the formation of fibrin, a critical factor in control of bleeding.[9] In the presence of tissue trauma and systemic hypoperfusion the process is disrupted, leading to the development of acute traumatic coagulopathy (ATC).[10] Continued blood loss, acidemia, hypothermia, consumption of clotting factors, and haemodilution resulting from resuscitation efforts can exacerbate the coagulation defect.[11] Approximately 25% of severely injured patients present with ATC[12 13], a condition associated with higher transfusion requirements, organ failure, septic complications, increased length of stay in the intensive care unit (ICU), and mortality.[14 15] Consequently, management of ATC has become a prominent issue in the care of trauma patients.[16] Tranexamic acid (TxA), an antifibrinolytic agent, has shown promise in hemorrhage control in adult trauma patients. As a synthetic derivative of the amino acid lysine, TxA competitively inhibits the activation of plasminogen to plasmin, a serine protease that breaks down fibrin and prevents blood clot formation.[17] In the large randomized CRASH-2 trial with over 20,000 participants 16 years of age and older, the use of TxA was associated with a significant reduction in mortality rates due to bleeding, and was demonstrated to be especially beneficial when administered within one hour of injury.[18 19] Survival benefits and reduced coagulopathy were also observed in the military setting, where the MATTERS I and II cohort studies of more than 2,000 combat casualties used

TxA in emergency resuscitation.[20 21] Neither study identified significant risks, such as increased thromboembolic events, associated with the administration of TxA.

Multiple studies in paediatric patients have demonstrated the benefits of TxA in major spine, cardiac and craniofacial surgeries. Meta-analyses on the uses of TxA in paediatric surgery concluded that the antifibrinolytic led to decreased blood loss and a reduced need for blood product transfusion.[22-25] However, the pathogenesis of traumatic hemorrhage differs significantly from non-traumatic surgical bleeding. During the former, tissue injuries are massive, uncontrolled, and patients commonly experience delays before receiving treatment.[24] While elective surgeries are performed in a controlled environment, where normothermia and normovolemia are maintained[26 27], hypothermia and hypovolemic shock are observed frequently in the traumatically injured patient.[28] It is therefore unlikely that the methods employed to control surgical bleeding will be directly applicable to the control of traumatic hemorrhage, and a knowledge synthesis that explores the specific role of TxA in paediatric trauma is warranted.

Recently, the PED-TRAX observational study of 766 injured patients 18 years of age or younger showed decreased mortality, improvements in discharge neurologic status, as well as decreased ventilator dependence in bleeding trauma patients treated with TxA compared with those who were not. Furthermore, no adverse safety- or medication-related complications were observed.[29] In recognition of the potential life-saving effects of TxA, the Royal College of Paediatrics and Child Health has issued a recommendation on a pragmatic dosage schedule for injured children.[30] The American Academy of Pediatrics, however, has not yet issued any official guidelines on the use of TxA in paediatric traumatic injury. While some children's hospitals have

integrated TxA into their mass transfusion protocols, a consensus on its timing and dosing has not yet been reached.[31 32]

This review proposes to address the observed gap in current paediatric trauma care by investigating the uses, benefits, and adverse effects of TxA in injured children. The synthesis will collate existing evidence on the efficacy of TxA and facilitate the development of novel trauma care pathways and policies directed at the injured child.

SYSTEMATIC REVIEW QUESTION

- What is the current evidence of effectiveness of TxA at reducing morbidity and mortality in traumatically injured children with hemorrhage?
- What are the current uses, benefits, dosing regimens and adverse effects of TxA compared with standard practice for controlling traumatic hemorrhage in paediatric patients?

METHODS AND ANALYSIS

This review will follow the guidelines and recommendations laid out by the Cochrane Collaboration[33] and will conform to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) (Supplementary Table 1). The review has been registered with PROSPERO under the identification code: CRD42016038023.

Eligibility criteria

Population

To be included, studies must describe participants younger than 18 years of age who have suffered any type of traumatic injury with hemorrhage. Studies of patients with pre-existing haematologic disorders will be excluded.

Intervention

Studies that describe the administration of any amount of TxA, whether intravenously as a bolus and/or infusion, to control hemorrhage in trauma patients younger than 18 years of age within the first 24 hrs after injury will be included. Studies that describe co-administration of other antifibrinolytic agents with TxA will be excluded, as this may confound results. Studies that describe the use of TxA in elective surgeries will be excluded.

Comparator

For inclusion, studies must contain a comparator group of paediatric trauma patients that have received routine measures to control hemorrhage or who have also received a placebo. Studies that compare different TxA dosing schemes and no placebo, or studies that compare the efficacy of TxA with other antifibrinolytics (e.g. ε-aminocaproic acid, recombinant factor VIIa, aprotinin) will also be considered.

Setting

Studies will not be restricted to location or setting. All circumstances where TxA was administered to bleeding trauma patients will be examined.

Types of study to be included

To be included studies must be randomized controlled trials (RCTs) or clinical trials. Cohort studies will be considered for inclusion, provided that data from a comparison group are reported. Case or series studies will be excluded due to the risk of bias associated with these study designs. Case-control studies, with the exceptions of those nested as part of a cohort study, will be excluded. Economic evaluation studies will be excluded.

OUTCOMES

The primary outcome of interest will be death within four weeks of injury. Secondary outcomes will include the number of units of blood products transfused, re-bleeding events, surgical intervention, and the occurrence of thrombo-embolic events. The method, dosing and timing of TxA administration will also be examined within subgroup analyses.

SEARCH STRATEGY

A search strategy was created with the aid of a research librarian and combines keywords and MeSH terms from three themes: the population (paediatric patients), the condition (trauma and hemorrhage) and the intervention (tranexamic acid) (Supplementary Table 2). Search terms were created both as keywords (title/abstract words) and subject headings (eg: MeSH) as appropriate. No language or publication date restrictions will be placed on the searches. The searches will be kept broad, and the search strategies created have incorporated neither study design filters, nor limitations on comparators or outcomes. Sources to be searched will include bibliographic databases (MEDLINE, EMBASE, PubMed, CINAHL, Cochrane CENTRAL); abstract and

conference proceedings resources [Web of Science Conference Proceedings Citation Index – Science (1990 – present)], Canadian Anesthesiologists' Society, Trauma Care Conference, The Canadian Association of Emergency Physicians]; and controlled trials registries (clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), ISRCTN registry, HKU Clinical Trials Registry, Clinical Trials Registry – India, UK Clinical Trials Gateway, Canadian Clinical Trials Database). Additional citations will be retrieved by scanning the reference lists of included studies and relevant reviews, and contacting authors of key publications and other experts in this field.

Study selection and quality assessment

Citations will be collected in a reference manager software program (EndNote) and duplicates will be eliminated by first using the CREBP Systematic Review Assistant tool (crebp-sra.com) and then manually. The full list of citations will be screened by two reviewers independently and in duplicate in two stages, the first restricted to citation titles and abstracts, followed by full-text review of included articles. Interrater agreement will be assessed through Cohen's kappa coefficient.[34] For this statistic, values <0.4 indicate poor agreement, 0.4-0.59 fair agreement, 0.60-0.74 good agreement, and >0.75 excellent agreement.[35] Discrepancies between the reviewers will be resolved by discussion or with the assistance of a third team member. Risk of bias assessment will be conducted using the recommendations and tools provided by the Cochrane Collaboration.[33]

Data extraction and analysis

Basic information about included studies will be collected (authors, journal, years of study and publication, location of study, study design, number of patients included, etc.). Patient demographics will be recorded along with type of injury and severity (e.g. injury severity score, Glasgow coma scale, etc.), and haemostatic measurements (e.g. prothrombin time, haemoglobin levels, clot lysis at 30 minutes, etc.). The method, timing, and dosing for TxA administration will be recorded. Outcome data to be abstracted will include mortality at 24 and 48 hrs, at four weeks post-injury, and at/before discharge, cause of death, blood product administration, incidence of thromboembolic events, re-bleeding and surgical intervention.

Data abstraction will be conducted by two reviewers independently and in duplicate with the aid of a standardized, piloted data extraction form. Disagreements between the two reviewers will be resolved through discussion or with the assistance of a third team member.

Data analysis will take the form of a narrative synthesis in which studies are described and categorized according to design and purpose. Sub-group analysis may involve stratification of studies by types of injury or TxA administration (bolus vs. continuous intravenous infusion) and dosage. A meta-analysis will be conducted if effect measures for individual studies are provided or can be calculated and if studies are suitably homogeneous. The degree of heterogeneity will be determined through a qualitative assessment of the clinical diversity and methodological heterogeneity. The degree of heterogeneity will be evaluated qualitatively as well as quantitatively through the use of the I^2 statistic: $I^2 = (Q-df/Q)x100\%$.

Meta-analysis using a random-effects model will be considered in the case of moderate or unimportant heterogeneity (I^2 less or equal to 60%). In the case of substantial heterogeneity, the

analysis will be restricted to the narrative synthesis exploring heterogeneity through subgroup analysis.

Confidence in cumulative evidence and assessment of Publication Bias

The GRADE system will be employed to assess the quality of the evidence presented across the studies included for review.[36] Depending on design, methods and execution, consistency, and directness of evidence, quality of evidence from each study will be rated as high, moderate, low, or very low by two independent reviewers. Disagreements will be resolved through discussion or with the assistance of a third team member. The GRADE system will also be employed to evaluate any recommendations that will arise from this review.

Publication bias will be assessed through visual inspection of the Begg's funnel plot and through the use of Egger's test.

DISCUSSION

This knowledge synthesis proposes to collate existing evidence on the current uses, safety and effectiveness of TxA in the control of hemorrhage in injured children. We anticipate that our data synthesis will provide sufficient information to inform trauma care pathways and assist clinicians caring for paediatric trauma patients. Finally, this systematic review will help expand our understanding of the uses, benefits and harms of antifibrinolytic drugs in the bleeding trauma patient and identify areas where gaps in knowledge remain.

AUTHORS' CONTRIBUTIONS

DU developed and wrote the review protocol and will write the final manuscript. DLL assisted with the design of the search strategy. MB assisted with formulating the aims and objectives of

the study and assisted in study design including determination of the inclusion and exclusion criteria. IWYM has aided in study design including planning statistical analysis. RD, JG, MCP, MS, and DLL aided in setting the aims and objectives of this study. All authors have aided in review and revision of this manuscript and approve of it in its current form.

FUNDING STATEMENT

Research reported in this publication is supported by the Alberta Health Services Emergency Strategic Clinical Network (ESCN) 2016 Systematic Review Grant and also the Brian and Brenda MacNeill Chair in Pediatric Surgery through the EQuIS quality and safety research platform. The content is solely the responsibility of the authors and does not necessarily represent the official views of the ESCN Scientific Office, the MacNeill family, or Alberta Health Services.

COMPETING INTERESTS

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the quality or the presentation of the work described in this manuscript.

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Supplementary Table 1. 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 #	CHECKLIST ITEM	CHECK
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	☒
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☒
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	☒
Sponsor	5b	Provide name for the review funder and/or sponsor	☒
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	☒
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☒
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	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☒
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☒
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☒
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	☒
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☒
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☒
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☒

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ABSTRACT

Introduction: Trauma is the leading cause of death among children aged 1-18. Studies indicate that better control of bleeding could potentially prevent 10-20% of trauma-related deaths. The antifibrinolytic agent tranexamic acid (TxA) has shown promise in hemorrhage control in adult trauma patients. However, information on the potential benefits of TxA in children remains sparse. This review proposes to evaluate the current uses, benefits and adverse effects of TxA in the bleeding paediatric trauma population.

Methods and analysis: A structured search of bibliographic databases (e.g. Medline, EMBASE, PubMed, CINAHL, Cochrane CENTRAL) has been undertaken to retrieve randomized controlled trials (RCTs) and cohort studies that describe the use of TxA in paediatric trauma patients. To ensure that all relevant data were captured, the search did not contain any restrictions on language or publication time. After deduplication, citations will be screened independently by two authors, and selected for inclusion based on pre-specified criteria. Data extraction and risk of bias assessment will be done independently and in duplicate. Meta-analytic methods will be employed wherever appropriate.

Ethics and dissemination: This study will not involve primary data collection, and formal ethical approval will therefore not be required. The findings of this study will be disseminated through a peer-reviewed publication and at relevant conference meetings.

PROSPERO registration number: CRD42016038023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is the first systematic review to evaluate the uses and efficacy of tranexamic acid (TxA) in paediatric trauma patients.
- This study has a great potential for translation as current protocols in pediatric trauma are extrapolated from adult studies or generated from small diverse pediatric studies.
- The aims and objectives of this study were set by relevant stakeholders including a paediatric surgeon, a paediatric anesthesiologist, a paediatric emergency physician, and two hematologists.
- We anticipate that there will be few trials specifically evaluating the use of TxA in pediatric trauma patients and the numbers of patients within studies are likely to be small. The data available may be heterogenous and not suitable for meta-analysis.

INTRODUCTION

Trauma is a substantial cause of morbidity and mortality in both developed and developing countries.[1-3] In 2013, 973 million people worldwide sustained injuries that required medical attention and 4.8 million of these died from their injuries.[4] Trauma represents the leading cause of death and potential years of life lost (PYYL) among children and youth under the age of 18 years.[5 6] In 2004 an estimated 950,000 children under the age of 18 died of an injury world-

wide.[6] In the United States in 2012, 6.8 million children 18 years of age and younger were treated for trauma-related disorders, resulting in a total medical expenditure of US$7.8 billion.[7]

Hemorrhage continues to be a significant contributor to trauma-related death[8]. Studies indicate that better control of bleeding could prevent 10-20% of these deaths.[9] Vascular injury normally triggers coagulation, a complex proteolytic cascade that culminates in the formation of fibrin, a critical factor in control of bleeding.[10] In the presence of tissue trauma and systemic hypoperfusion the process is disrupted, leading to the development of acute traumatic coagulopathy (ATC).[11] Continued blood loss, acidemia, hypothermia, consumption of clotting factors, and haemodilution resulting from resuscitation efforts can exacerbate the coagulation defect.[12] Approximately 25% of severely injured patients present with ATC[13 14], a condition associated with higher transfusion requirements, organ failure, septic complications, increased length of stay in the intensive care unit (ICU), and mortality.[15 16] Consequently, management of ATC has become a prominent issue in the care of trauma patients.[17] Tranexamic acid (TxA), an antifibrinolytic agent, has shown promise in hemorrhage control in adult trauma patients. As a synthetic derivative of the amino acid lysine, TxA competitively inhibits the activation of plasminogen to plasmin, a serine protease that breaks down fibrin and prevents blood clot formation.[18] In the large randomized CRASH-2 trial with over 20,000 participants 16 years of age and older, the use of TxA was associated with a significant reduction in mortality rates due to bleeding, and was demonstrated to be especially beneficial when administered within one hour of injury.[19 20] Survival benefits and reduced coagulopathy were also observed in the military setting, where the MATTERS I and II cohort studies of more than 2,000 combat casualties used

TxA in emergency resuscitation.[21 22] Neither study identified significant risks, such as increased thromboembolic events, associated with the administration of TxA.

Multiple studies in paediatric patients have demonstrated the benefits of TxA in major spine, cardiac and craniofacial surgeries. Meta-analyses on the uses of TxA in paediatric surgery concluded that the antifibrinolytic led to decreased blood loss and a reduced need for blood product transfusion.[23-26] However, the pathogenesis of traumatic hemorrhage differs significantly from non-traumatic surgical bleeding. During the former, tissue injuries are massive, uncontrolled, and patients commonly experience delays before receiving treatment.[25] While elective surgeries are performed in a controlled environment, where normothermia and normovolemia are maintained[27 28], hypothermia and hypovolemic shock are observed frequently in the traumatically injured patient.[29] It is therefore unlikely that the methods employed to control surgical bleeding will be directly applicable to the control of traumatic hemorrhage, and a knowledge synthesis that explores the specific role of TxA in paediatric trauma is warranted.

Recently, the PED-TRAX observational study of 766 injured patients 18 years of age or younger showed decreased mortality, improvements in discharge neurologic status, as well as decreased ventilator dependence in bleeding trauma patients treated with TxA compared with those who were not. Furthermore, no adverse safety- or medication-related complications were observed.[30] In recognition of the potential life-saving effects of TxA, the Royal College of Paediatrics and Child Health has issued a recommendation on a pragmatic dosage schedule for injured children.[31] The American Academy of Pediatrics, however, has not yet issued any official guidelines on the use of TxA in paediatric traumatic injury. While some children's hospitals have

integrated TxA into their mass transfusion protocols, a consensus on its timing and dosing has not yet been reached.[8 32]

This review proposes to address the observed gap in current paediatric trauma care by investigating the uses, benefits, and adverse effects of TxA in injured children. The synthesis will collate existing evidence on the efficacy of TxA and facilitate the development of novel trauma care pathways and policies directed at the injured child. There is likely to be a small number of studies that meet inclusion criteria but the PED-TRAX study represents at least one large cohort study that should be included within the synthesis[30].

SYSTEMATIC REVIEW QUESTION

- What is the current evidence of effectiveness of TxA at reducing morbidity and mortality in traumatically injured children with hemorrhage?
- What are the current uses, benefits, dosing regimens and adverse effects of TxA compared with standard practice for controlling traumatic hemorrhage in paediatric patients?

METHODS AND ANALYSIS

This review will follow the guidelines and recommendations laid out by the Cochrane Collaboration[33] and will conform to the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)

(Supplementary Table 1). The review has been registered with PROSPERO under the identification code: CRD42016038023.

Eligibility criteria

Population

To be included, studies must describe participants younger than 18 years of age who have suffered any type of traumatic injury with hemorrhage. Studies of patients with pre-existing haematologic disorders will be excluded.

Intervention

Studies that describe the administration of any amount of TxA, whether intravenously as a bolus and/or infusion, to control hemorrhage in trauma patients younger than 18 years of age within the first 24 hrs after injury will be included. Studies that describe co-administration of other antifibrinolytic agents with TxA will be excluded, as this may confound results. Studies that describe the use of TxA in elective surgeries will be excluded.

Comparator

For inclusion, studies must contain a comparator group of paediatric trauma patients that have received routine measures to control hemorrhage or who have also received a placebo. Studies that compare different TxA dosing schemes and no placebo, or studies that compare the efficacy of TxA with other antifibrinolytics (e.g. ε-aminocaproic acid, recombinant factor VIIa, aprotinin) will also be considered.

Setting

Studies will not be restricted to location or setting. All circumstances where TxA was administered to bleeding trauma patients will be examined.

Types of study to be included

To be included studies must be randomized controlled trials (RCTs) or clinical trials. Cohort studies will be considered for inclusion, provided that data from a comparison group are reported. Case or series studies will be excluded due to the risk of bias associated with these study designs. Case-control studies, with the exceptions of those nested as part of a cohort study, will be excluded. Economic evaluation studies will be excluded.

OUTCOMES

The primary outcome of interest will be death within four weeks of injury. Secondary outcomes will include the number of units of blood products transfused, re-bleeding events, surgical intervention, and the occurrence of thrombo-embolic events. The method, dosing and timing of TxA administration will also be examined within subgroup analyses.

SEARCH STRATEGY

A search strategy was created with the aid of a research librarian and combines keywords and MeSH terms from three themes: the population (paediatric patients), the condition (trauma and hemorrhage) and the intervention (tranexamic acid) (Supplementary Table 2). Search terms were created both as keywords (title/abstract words) and subject headings (eg: MeSH) as appropriate. No language or publication date restrictions will be placed on the searches. The searches will be

kept broad, and the search strategies created have incorporated neither study design filters, nor limitations on comparators or outcomes. Sources to be searched will include bibliographic databases (MEDLINE, EMBASE, PubMed, CINAHL, Cochrane CENTRAL); abstract and conference proceedings resources [Web of Science Conference Proceedings Citation Index – Science (1990 – present)], Canadian Anesthesiologists' Society, Trauma Care Conference, The Canadian Association of Emergency Physicians]; and controlled trials registries (clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), ISRCTN registry, HKU Clinical Trials Registry, Clinical Trials Registry – India, UK Clinical Trials Gateway, Canadian Clinical Trials Database). Additional citations will be retrieved by scanning the reference lists of included studies and relevant reviews, and contacting authors of key publications and other experts in this field.

Study selection and quality assessment

Citations will be collected in a reference manager software program (EndNote) and duplicates will be eliminated by first using the CREBP Systematic Review Assistant tool (crebp-sra.com) and then manually. The full list of citations will be screened by two reviewers independently and in duplicate in two stages, the first restricted to citation titles and abstracts, followed by full-text review of included articles. Interrater agreement will be assessed through Cohen's kappa coefficient.[34] For this statistic, values <0.4 indicate poor agreement, 0.4-0.59 fair agreement, 0.60-0.74 good agreement, and >0.75 excellent agreement.[35] Discrepancies between the reviewers will be resolved by discussion or with the assistance of a third team member. Risk of bias assessment will be conducted using the recommendations and tools provided by the Cochrane Collaboration.[33]

Data extraction and analysis

Basic information about included studies will be collected (authors, journal, years of study and publication, location of study, study design, number of patients included, etc.). Patient demographics will be recorded along with type of injury and severity (e.g. injury severity score, Glasgow coma scale, etc.), and haemostatic measurements (e.g. prothrombin time, haemoglobin levels, clot lysis at 30 minutes, etc.). The method, timing, and dosing for TxA administration will be recorded. Outcome data to be abstracted will include mortality at 24 and 48 hrs, at four weeks post-injury, and at/before discharge, cause of death, blood product administration, incidence of thromboembolic events, re-bleeding and surgical intervention.

Data abstraction will be conducted by two reviewers independently and in duplicate with the aid of a standardized, piloted data extraction form. Disagreements between the two reviewers will be resolved through discussion or with the assistance of a third team member.

Data analysis will take the form of a narrative synthesis in which studies are described and categorized according to design and purpose. Sub-group analysis may involve stratification of studies by types of injury or TxA administration (bolus vs. continuous intravenous infusion) and dosage. A meta-analysis will be conducted if effect measures for individual studies are provided or can be calculated and if studies are suitably homogeneous. The degree of heterogeneity will be determined through a qualitative assessment of the clinical diversity and methodological heterogeneity. The degree of heterogeneity will be evaluated qualitatively as well as quantitatively through the use of the I^2 statistic: $I^2 = (Q\text{-}df/Q)x100\%$.

Meta-analysis using a random-effects model will be considered in the case of moderate or unimportant heterogeneity (I^2 less or equal to 60%). In the case of substantial heterogeneity, the analysis will be restricted to the narrative synthesis exploring heterogeneity through subgroup analysis.

Confidence in cumulative evidence and assessment of Publication Bias

The GRADE system will be employed to assess the quality of the evidence presented across the studies included for review.[36] Depending on design, methods and execution, consistency, and directness of evidence, quality of evidence from each study will be rated as high, moderate, low, or very low by two independent reviewers. Disagreements will be resolved through discussion or with the assistance of a third team member. The GRADE system will also be employed to evaluate any recommendations that will arise from this review.

Publication bias will be assessed through visual inspection of the Begg's funnel plot and through the use of Egger's test.

DISCUSSION

This knowledge synthesis proposes to collate existing evidence on the current uses, safety and effectiveness of TxA in the control of hemorrhage in injured children. We anticipate that our data synthesis will provide sufficient information to inform trauma care pathways and assist clinicians caring for paediatric trauma patients. Finally, this systematic review will help expand our understanding of the uses, benefits and harms of antifibrinolytic drugs in the bleeding trauma patient and identify areas where gaps in knowledge remain.

AUTHORS' CONTRIBUTIONS

DU developed and wrote the review protocol and will write the final manuscript. DLL assisted with the design of the search strategy. MB assisted with formulating the aims and objectives of the study and assisted in study design including determination of the inclusion and exclusion criteria. IWYM has aided in study design including planning statistical analysis. RD, JG, MCP, MS, and DLL aided in setting the aims and objectives of this study. All authors have aided in review and revision of this manuscript and approve of it in its current form.

FUNDING STATEMENT

Research reported in this publication is supported by the Alberta Health Services Emergency Strategic Clinical Network (ESCN) 2016 Systematic Review Grant and also the Brian and Brenda MacNeill Chair in Pediatric Surgery through the EQuIS quality and safety research platform. The content is solely the responsibility of the authors and does not necessarily represent the official views of the ESCN Scientific Office, the MacNeill family, or Alberta Health Services.

COMPETING INTERESTS

The authors declare that they have no significant competing financial, professional or personal interests that might have influenced the quality or the presentation of the work described in this manuscript.

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Supplementary Table 2. Sample OVID-Medline search strategy

1. exp tranexamic acid/	29. emergenc*.ti,ab,kw.
2. TxA.ti,ab,kw.	30. exp Emergency Medical Services/
3. cyklokapron.ti,ab,kw.	31. emergency medical services.ti,ab,kw.
4. lysteda.ti,ab,kw.	32. EMS.ti,ab,kw.
5. amca.ti,ab,kw.	33. exp Intensive Care/
6. AMCHA.ti,ab,kw.	34. exp Intensive Care Units/
7. transamin.ti,ab,kw.	35. intensive care.ti,ab,kw.
8. cyclohexanecarboxylic.ti,ab,kw.	36. ICU.ti,ab,kw.
9. t-amcha.ti,ab,kw.	37. exp Shock/
10. tranexamic.ti,ab,kw.	38. Shock.ti,ab,kw.
11. transexamic.ti,ab,kw.	39. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
12. ugurol.ti,ab,kw.	40. exp Pediatrics/
13. cyclocapron.ti,ab,kw.	41. exp Child/
14. cyclokapron.ti,ab,kw.	42. exp Infant/
15. cyklocapron.ti,ab,kw.	43. exp Infant, Newborn/
16. exacyl.ti,ab,kw.	44. p*edia*.ti,ab,kw.
17. anvitoff.ti,ab,kw.	45. child*.ti,ab,kw.
18. amchafibrin.ti,ab,kw.	46. infan*.ti,ab,kw.
19. KABI 2161.ti,ab,kw.	47. neonat*.ti,ab,kw.
20. spotof.ti,ab,kw.	48. newborn.ti,ab,kw.
21. trans4aminomethylcyclohexanecarboxylic acid.ti,ab,kw.	49. juvenile.ti,ab,kw.
22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	50. adolescen*.ti,ab,kw.
23. exp "Wounds and Injuries"/	51. exp Adolescent/
24. trauma.ti,ab,kw.	52. exp Young Adult/
25. injur*.ti,ab,kw.	53. young adult.ti,ab,kw.
26. wound.ti,ab,kw.	54. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
27. fractur*.ti,ab,kw.	55. 22 and 39 and 54
28. exp Emergencies/	

Supplementary Table 1. 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 #	CHECKLIST ITEM	CHECK
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	☒
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☒
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	☒
Sponsor	5b	Provide name for the review funder and/or sponsor	☒
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	☒
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☒
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	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☒
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☒
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☒
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	☒
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☒
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☒
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☒