Does the intraoperative administration of tranexamic acid (TXA) increase the incidence of deep venous thrombosis in total knee arthroplasty?

PROTOCOL TITLE:

Does the intraoperative administration of tranexamic acid (TXA) increase the incidence of deep venous thrombosis in total knee arthroplasty?

Short title: Tranexamic acid and blood clots in knee surgery

PRINCIPAL INVESTIGATOR:

David Siegel, MD
Anesthesiology & Critical Care Medicine

VERSION NUMBER:

3.

DATE:

August 3, 2017.

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☒	HHS (Department of Health and Human Services)
☐	Other:

Is this a clinical trial under ICH-GCP E6? ☐ Yes ☒ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☐ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

1.1. The purpose of this study is to estimate the incidence of diagnosable deep-vein thrombosis (DVT) in total knee arthroplasty (TKA) patients after administration of tranexamic acid (TXA).

1.2. The hypothesis is that intraoperative administration of TXA will increase the incidence of DVT as detected by lower-extremity ultrasound on postoperative day 1 in TKA patients when compared to the historic incidence of this complication in patients not administered TXA.

2. Background

2.1. The administration of the anti-fibrinolytic agent tranexamic acid (TXA) to prevent bleeding and transfusion has become commonplace in a variety of clinical settings following the publication of many studies documenting its efficacy (1-4). However, questions remain regarding the safety of this agent in known thrombogenic settings such as total joint arthroplasty. Because TXA directly inhibits the activation of plasmin, an increase in risk of pathologic thrombosis is possible. Safety claims to date for TXA are based upon secondary outcomes of clinically apparent deep venous thrombosis/pulmonary embolus (DVT/PE) between treated and control groups in studies designed primarily to assess blood loss (5,6). None have prospectively examined the risk of DVT as a primary outcome in patients treated with TXA in total joint arthroplasty. Furthermore, most studies have only used the presence of clinically apparent DVT to define the complication, which is known to significantly underestimate the true incidence (13). This lack of safety data has been noted by the author of a recent meta-analysis of TXA, who concluded: "The effect of tranexamic acid on thromboembolic events remains uncertain"(1). Conversely, a recent retrospective study of total hip arthroplasty patients using screening lower extremity ultrasound did show a significant increase in DVT in the TXA treated patients (8). Case reports of DVT, myocardial infarction and PE temporally associated with TXA administration continue to accumulate (9-11). Clearly, the safety of routine TXA administration remains a topic of concern.

2.2. The investigators have not obtained any preliminary data.

3. Study Design

3.1. This is a prospective observational study.

3.2. This is an open-label study.

4. Inclusion and Exclusion Criteria

4.1. Participants will be recruited from among those presenting for total knee arthroplasty (joint replacement) at UNM Sandoval Regional Medical Center.

4.2. Inclusion criteria include:

- Age >18 years

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- Scheduled for total knee arthroplasty at SRMC with administered tranexamic acid, according to UNM Orthopedic Surgery protocol

Exclusion criteria:

- Previous deep vein thrombosis or pulmonary embolism episode
- Known coronary artery disease or peripheral vascular disease
- Previously diagnosed hypercoagulable states (e.g. Leiden factor V, antiphospholipid antibody, protein C or S deficiency)
- Pregnancy
- Creatinine clearance less than 30 ml/min
- Non-fluency in English

4.3. This study will not include participants from the special populations of: adults unable to consent, individuals who are not yet adults, pregnant women, or prisoners.

4.4. The investigators will not enroll participants who are not fluent in English. Funding for this study is limited, and thus its study size is small. If the investigators were to obtain translation for the consent/HIPAA documentation, the cost of that service would have a substantial adverse effect on the available sample size and thus on study power, likely rendering its findings uninterpretable. Also, there is not a substantial *a priori* reason to suspect that language skills themselves have any effect on postoperative thrombotic risk, so the investigators believe that this exclusion will not adversely affect the rights of Spanish-speaking people to enjoy the benefits of clinical research. Because this exclusion will not present an injustice, but will serve to preserve study validity, the investigators plan to exclude non-English speakers.

5. Number of Subjects

5.1. We currently plan to complete data collection for 30 patients for this study, but may extend it to 100. With traditional thresholds of 80% power and α=0.05, 30 patients should be sufficient to detect a statistically-significant increase in DVT rate from the historic 12% to approximately 32%. The investigators are seeking additional funding to further refine the actual incidence of post-TKR DVT, and if this funding is obtained may extend the study to 100 patients. Due to dropouts and exclusions, we may enroll up to 50 patients in order to complete data collection on the planned initial sample of 30.

6. Study Timelines

6.1.

- Individual subjects will be involved in the research on two consecutive days: they will provide consent on the day of surgery, and receive an ultrasound scan for deep vein thrombosis on postoperative day 2.
- The investigators estimate that approximately 10 participants per month will choose to enroll in this study; hence enrollment is estimated to take approximately 3 months.

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- Upon completion of enrollment and data collection, analysis and manuscript preparation are estimated to take one year.

7. Study Endpoints

7.1. The primary study outcome is the incidence of deep vein thrombosis observed by lower-extremity ultrasound on postoperative day 2. The investigators have not identified secondary outcomes.

7.2. The investigators have not identified safety outcomes. The only modification to routine practice that is entailed in this study is the administration of an ultrasound scan for lower-extremity preclinical DVT.

8. Research Setting

8.1. All study activities will occur in the context of normal medical treatment at UNM SRMC, including recruitment/consent, medical treatment, and ultrasonography.

8.2. Potential subjects will be identified from among investigators' routine patients. Recruitment will occur in the preoperative holding areas at SRMC, where the preoperative anesthesia consultation already occurs.

8.3. The ultrasound scan for thrombosis will occur in the patient's room on postoperative day 2. The scan will be read by appropriate Radiology personnel in their offices soon thereafter.

9. Resources Available

9.1. Investigators Drs. David Siegel and Neal Gerstein are faculty members in the Department of Anesthesiology with substantial research experience. Investigator Dr. Brad Cushnyr is a faculty member in the Department of Radiology and the Chief of Radiology at SRMC. Investigator Tim Petersen PhD is a member of the Anesthesiology department and routinely advises that department's researchers.

9.2. All medical decisions will be made by licensed providers in accordance with their routine job duties. This is an observational trial and does not involve any manipulation of patient treatment for research purposes.

9.3. Other resources:

- Approximately 250 one-sided knee replacement surgeries are performed annually at SRMC. The investigators estimate that approximately 10 per month would consent to participate.
- Investigators will conduct this study and associated activities as part of their routine job duties.

10. Prior Approvals

10.1. The Departmental Review Form is included with this application.

10.2. The Drug Attachment is included with this application.

11. Multi-Site Research

11.1. This is not multi-site research.

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12.Study Procedures

12.1.

- Subjects included in the study will have ultrasonic (US) examination of their lower extremity veins performed on postoperative day #2 by an authorized ultrasound technician. The US examination will be interpreted by one of the investigators (Dr. Cushynr) for the presence or absence of deep and superficial venous thrombosis. No other investigations are planned.
- Each patient will have been scheduled for elective total knee replacement, which by protocol at our institution includes the administration of tranexamic acid (TXA). Some surgeons administer it intravenously, and others use intra-articular administration during surgery. The use of this medication is not modified by the existence of this research study. Other than the study intervention (bilateral lower extremity US examination) described above, no alteration in the patient's perioperative care will occur as a result of the study. The use of TXA for this purpose is widespread in orthopedic surgery but is technically off-label.
- The main data source will be the stored ultrasound images and the associated radiologic interpretations, provided in a routine radiology report.
- Patients undergoing total knee arthroplasty who develop clinical evidence of deep venous thrombosis (pain, swelling, redness in the lower extremity) or evidence of pulmonary embolus would be referred for ultrasound of the lower extremity regardless of study participation. Conversely, each study patient who is found to have an asymptomatic DVT on US on postoperative day 2 will be referred to their orthopedic surgeon for appropriate management. This management may include medical or intravascular therapy, as appropriate in the clinical judgment of the physicians involved.

13.Data Analysis

13.1. The primary outcome (rate of development of DVT) will be analyzed with a binomial test of proportion. The null hypothesis is that the one-sided 95% confidence interval around the observed rate of DVT will include the historic rate of 12%. The alternate hypothesis is that this 95% confidence interval will be higher than and exclude 12%.

13.2. With traditional thresholds of 80% power and α=0.05, 30 patients should be sufficient to detect an increase in DVT rate from the historic 12% to approximately 32% with statistical significance.

14.Provisions to Monitor the Data to Ensure the Safety of Subjects

This section is required when research involves more than Minimal Risk to subjects. Describe:

14.1. This is an observational trial, so participation in this study does not increase patient risk. This study does not modify patients' surgical experience, drugs administered, route of administration, or any other component of surgery. The only change from routine practice is the addition of a screening exam.

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15. Withdrawal of Subjects

15.1. The investigators have not identified any likely circumstances in which subjects may be withdrawn from the study without their consent. They may do so, however, if in their opinion this action would be best for participants or for the study. An exhaustive listing of these unlikely situations is not possible, but one example would be a disruptive patient.

15.2. As it does not involve treatment, this study does not include a plan for orderly termination/safe withdrawal.

15.3. This study involves a single ultrasound scan after routine surgery. Partial withdrawal is not practical.

15.4. If a subject withdraws, existing data will be maintained but with a note indicating that withdrawal.

16. Data Management/Confidentiality

16.1. Investigators include physicians who treat prospective subjects as part of their routine job duties.

16.2. The research requires the use of direct identifiers in order to accurately match scans to patients. The scans and the surgical information constitute Protected Health Information.

16.3. The data do not include information that is usually considered "sensitive."

16.4. The investigators do not plan to obtain a Certificate of Confidentiality.

16.5. Data will be maintained in locked files in secure areas. All electronic data will be maintained on UNM HSC secure password-protected servers. All investigators are HIPAA-certified and have completed CITI training.

16.6. Data will not be collected or transmitted via the internet.

16.7. The data do not include audio or video recordings, or photographs.

17. Data and Specimen Banking

17.1. Deidentified data may be stored indefinitely to serve as underlying data to inform future studies, such as for sample size estimation.

18. Risks to Subjects

18.1. Ultrasound scans do not involve substantial risk. It is possible that some patients' scans may indicate underlying health conditions that are not known at the time of the scan. All scans involve the lower extremity, so this probability is low.

18.2. The investigators have minimized risk by selecting an observational strategy and by using ultrasound for the DVT scans.

19. Potential Benefits to Subjects

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19.1. The scans may indicate pre-clinical thrombosis and allow the patient to obtain antithrombotic treatment earlier than would otherwise be available.

20. Recruitment Methods

20.1. Patients will be recruited in the preoperative holding areas at SRMC, during the preoperative anesthesia consultation.

20.2. Potential subjects will be identified from among investigators' regularly scheduled patients.

20.3. Other than the consent/HIPAA materials, there will not be any recruitment materials.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. Recruitment and consent discussions will occur in the context of the preoperative anesthesia consultation, which is already handled in a private/confidential manner. Investigators will first ask whether potential subjects are interested in participating in a study, and if so, the details will be discussed and the consent material introduced.

22. Economic Burden to Subjects

22.1.

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
Ultrasonographic scan of lower extremity	All	☒	☐
Radiology services (read scan)	All	☒	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Surgery, hospitalization, medications	All	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐

22.2. Patients or 3rd-party payers will be responsible for any costs related to adverse events.

23. Compensation

23.1. Participants will not be compensated.

24. Compensation for Research-Related Injury

24.1. This is a minimal-risk study.

25. Consent Process

25.1. The investigators will obtain consent prior to research-related activity.

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25.1.1. An investigator will obtain consent. All investigators are HIPAA-certified and have completed CITI training.

25.1.2. The consent process will occur in the preoperative holding areas of SRMC.

25.1.3. Prospective participants will be assured that participation is voluntary.

25.1.4. As this is an observational study, prospective participants should not need much time to consider participation. Those who cannot decide in the available time will be excused from participation.

25.1.5. Consent will be assumed to be ongoing for the purpose of the scan on postoperative day 2 unless the subject objects to the scan.

25.1.6. The consenting investigator will ask subjects to describe the study in their own words, and will correct any misunderstandings.

Subjects not fluent in English

25.1.7. This is a low-enrollment study; the investigators do not plan to enroll non-English speakers.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative

25.1.8. This study does not involve cognitively impaired adults or those unable to consent.

Subjects who are not yet adults (infants, children, teenagers)

25.1.9. The study does not involve subjects who are not yet adults.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

- We are not requesting waiver or alteration of the consent process.

26. Documentation of Consent

26.1. A consent/HIPAA form is included with this application. Only consenting patients will be enrolled.

27. Study Test Results/Incidental Findings

27.1. **Individual Results:** Individual results will be shared with participants inasmuch as they will be kept apprised of their condition by relevant medical personnel; a DVT is a medical condition that would be brought to the attention of the patient. As noted in section 12 above, this treatment may involve medical or intravascular treatment as appropriate, depending on the clinical judgment of the physicians involved.

27.2. **Incidental Findings:** The radiologist who reads the ultrasound scan will report any incidental findings to an investigator or the patient's surgeon for followup. The exact nature of this followup depends on the nature of the incidental

finding. It is left to the clinical judgment of the physicians involved, and discussed with the patient as appropriate.

28. Sharing Study Progress or Results with Subjects

28.1. The investigators do not plan to share partial study results with subjects. Similarly, the investigators do not plan to keep patient identifiers or contact information beyond completion of data collection, so it will not be possible to contact subjects with final study results. In any event, the outcome of interest will have either occurred or not occurred for each subject, so the experiences of others will not be useful information to the subjects.

29. Inclusion of Vulnerable Populations

29.1. The study does not include vulnerable populations. Some subjects may be students or employees of UNM or UNM HSC, but these are not specifically targeted or excluded.

30. Community-Based Participatory Research

30.1. This study does not involve community-based participatory research.

31. Research Involving American Indian/Native Populations

31.1. American Indian/Native persons may be incidentally enrolled in this study, but they are not specifically targeted or excluded.

32. Transnational Research

32.1. This study does not involve transnational research.

33. Drugs or Devices

33.1. Tranexamic acid is approved by the FDA, but is off-label for the usage described above. This study does not modify its usage in any way. The investigators have not sought an IND.

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Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

NA; we are not seeking this waiver or alteration.

II. Vulnerable Populations

NA; this study does not involve these populations.

III. Medical Devices

NA; this is not a device study.