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Authors

Nishijima, Daniel K

VanBuren, John M

Linakis, Seth W

et al.

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Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): a pilot randomized trial

Daniel K. Nishijima, MD, MAS,
Department of Emergency Medicine, UC Davis School of Medicine, 4150 V. Street, PSSB 2100, Sacramento, CA 95817

John M. VanBuren, PhD,
Department of Pediatrics, University of Utah School of Medicine, 295 Chipeta Way, Salt Lake City, UT 84108

Seth W. Linakis, MD,
Department of Pediatrics, Division of Pediatric Emergency Medicine, Ohio State University School of Medicine, Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205

Hilary A. Hewes, MD,
Department of Pediatrics, Division of Pediatric Emergency Medicine, University of Utah School of Medicine, Primary Children's Hospital, 100 N. Mario Capecchi Dr., Salt Lake City, UT 84113

Sage R. Myers, MD, MSCE,
Department of Pediatrics, Division of Pediatric Emergency Medicine, Perelman School of Medicine at the University of Pennsylvania, Children's Hospital of Philadelphia, 3401 Civic Center Blvd., Philadelphia, PA 19104

Matthew Bobinski, MD, PhD,
Department of Radiology, UC Davis School of Medicine, 2315 Stockton Blvd., Sacramento, CA 95817

Nam K. Tran, PhD, HCLD (ABB),
Department of Pathology and Laboratory Medicine, University of California, Davis, 4400 V. Street, Sacramento, CA 95816

Simona Ghetti, PhD,
Department of Psychology, University of California, Davis, 102K Young Hall, 1 Shields Ave., Davis, CA 95616

P. David Adelson, MD,
Department of Pediatric Neurosciences, Barrow Neurological Institute at Phoenix Children's Hospital, 1919 E. Thomas Rd, Phoenix, AZ 85016

Ian Roberts, MB, BCh, FRCP, FPH,

Corresponding Author: Daniel Nishijima, MD, MAS, University of California, Davis Medical Center, 4150 V. St. PSSB, 2100, Sacramento, CA 95817, TEL (916) 734.3884, FAX (916) 734.7950, dnishijima@ucdavis.edu.
See additional authors under Acknowledgements

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The authors declare that they have no competing interests currently.

Clinical Trials Unit, London School of Hygiene and Tropical Medicine, Keppel Street, WC1E 7HT, London, UK

James F. Holmes, MD, MPH,
Department of Emergency Medicine, UC Davis School of Medicine, 4150 V. Street, PSSB 2100, Sacramento, CA 95817

Walton O. Schalick III, MD, PhD,
Department of Orthopedics and Rehabilitation, University of Wisconsin, 317 Knutson Drive, Madison, WI 53704

J. Michael Dean, MD, MBA,
Department of Pediatrics, University of Utah School of Medicine, 295 Chipeta Way, Salt Lake City, UT 84108

T. Charles Casper, PhD,
Department of Pediatrics, University of Utah School of Medicine, 295 Chipeta Way, Salt Lake City, UT 84108

Nathan Kuppermann, MD, MPH,
Departments of Emergency Medicine and Pediatrics, UC Davis School of Medicine, 4150 V. Street, PSSB 2100, Sacramento, CA 95817

TIC-TOC Collaborators of the Pediatric Emergency Care Applied Research Network (PECARN)

Abstract

Background: The antifibrinolytic drug tranexamic acid (TXA) improves survival in adults with traumatic hemorrhage; however, the drug has not been evaluated in a trial in injured children. We assessed the feasibility of a large-scale trial evaluating the effects of TXA in children with severe hemorrhagic injuries.

Methods: Severely injured children (0 up to 18th birthday) were randomized into a double-blind randomized trial of 1) TXA 15 mg/kg bolus dose, followed by 2 mg/kg/hr infusion over 8 hours, 2) TXA 30 mg/kg bolus dose, followed by 4 mg/kg/hr infusion over 8 hours, or 3) normal saline placebo bolus and infusion. The trial was conducted at 4 pediatric Level I trauma centers in the United States between June 2018 and March 2020. We enrolled patients under federal exception from informed consent (EFIC) procedures when parents were unable to provide informed consent. Feasibility outcomes included the rate of enrollment, adherence to intervention arms, and ability to measure the primary clinical outcome. Clinical outcomes included global functioning (primary), working memory, total amount of blood products transfused, intracranial hemorrhage progression, and adverse events. The target enrollment rate was at least 1.25 patients per site per month.

Results: A total of 31 patients were randomized with a mean age of 10.7 years (standard deviation [SD] 5.0 years) and 22 (71%) patients were male. The mean time from injury to randomization was 2.4 hours (SD 0.6 hours). Sixteen (52%) patients had isolated brain injuries and 15 (48%) patients had isolated torso injuries. The enrollment rate using EFIC was 1.34 patients per site per month. All eligible enrolled patients received study intervention (9 patients TXA 15 mg/kg bolus dose, 10 patients TXA 30 mg/kg bolus dose, and 12 patients placebo) and

had the primary outcome measured. No statistically significant differences in any of the clinical outcomes were identified.

Conclusion: Based on enrollment rate, protocol adherence, and measurement of the primary outcome in this pilot trial, we confirmed the feasibility of conducting a large-scale, randomized trial evaluating the efficacy of TXA in severely injured children with hemorrhagic brain and/or torso injuries using EFIC.

Trial registration: ClinicalTrials.gov registration number: NCT02840097. Registration date July 14, 2016.

Keywords

Pediatric trauma; Tranexamic Acid; Clinical Trial

BACKGROUND

Trauma is the leading cause of death and disability in children in the United States (U.S.) with the major contributors being hemorrhagic brain and torso injuries.[1,2] More than 12,000 children die annually (more than 30 children per day) from trauma in the U.S. and another 150,000 injured children who survive their injuries require prolonged hospitalizations and have long-term functional deficits.[3–5] Long-term functional outcomes are directly related to the extent of hemorrhage; more hemorrhage results in more interventions and complications, greater disability, and longer recovery in children.[6,7]

In the surgical setting, the antifibrinolytic agent tranexamic acid (TXA) successfully blocks plasmin-mediated fibrin clot breakdown and attenuates bleeding.[8,9] In adults with hemorrhagic torso injuries, the investigators of the Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage 2 (CRASH-2) trial randomized 20,211 patients to TXA or placebo. When administered within three hours of injury, TXA reduced death from bleeding by one-third and improved post-injury global functioning.[10,11] More recently, the CRASH-3 and the Resuscitation Outcomes Consortium (ROC) trials evaluated TXA in adults with traumatic brain injuries (TBI). Neither trial had statistically significant results but showed trends toward improved survival and functional outcomes in patients receiving TXA.[12,13]

Despite the results from prior TXA studies, important knowledge gaps remain regarding the efficacy and safety of TXA in injured children. The lack of randomized trials of TXA in children with hemorrhagic injuries has left clinicians unsure about its use. TXA is routinely given to severely injured children in the United Kingdom[14] and Europe[15] but not in the U.S.[16] Some experts have advocated for its routine use in children based on current data, while others have cautioned against it until pediatric-specific data are available.[17–19] Determining if TXA is beneficial and safe in injured children is a top priority for numerous stakeholders.[17–20]

Although specific strategies have been recommended to improve the efficiency of clinical trials, it is often difficult for investigators to identify all the potential obstacles to optimize trial efficiency before actually starting the trial.[21–23] Premature closure of phase 3 clinical

trials due to insufficient patient accrual wastes substantial time and resources, with great risk for Type II errors.[24–26] Pilot trials, designed to enroll a small number of patients with the primary goal of assessing the feasibility of a subsequent phase 3 trial, provide a less expensive alternative to prematurely embarking on a costly, large-scale trial.[27] Pilot studies conducted prior to definitive studies are particularly crucial for clinical trials of critically ill children, which by nature are at risk for low patient accrual and complex regulatory requirements. Our primary objective of this pilot trial was to evaluate the ability to efficiently identify and enroll children with severe hemorrhagic injuries into a multicenter, randomized trial evaluating two doses of TXA and placebo. This pilot trial would provide important information about the feasibility of a large scale, phase 3 efficacy trial.

METHODS

Study Design

We conducted a double-blind, randomized trial of children younger than 18 years with hemorrhagic injuries to the brain and/or torso (Protocol and CONSORT checklist included in Appendix). We planned to enroll a maximum of 40 children in this pilot trial, but due to research restrictions at enrolling sites during the COVID-19 pandemic, we stopped enrollment at 31 patients. This pilot study was conducted using the same anticipated study design and procedures, intervention arms, and outcomes as the subsequent planned large clinical trial of TXA for children with hemorrhagic torso and/or brain injuries.

Study Setting

The study was conducted at 4 sites between June 12, 2018 to March 25, 2020. All sites were American College of Surgery verified Level I pediatric trauma centers in the U.S. The study was approved by a single Institutional Review Board at the University of Utah and with the U.S. Food and Drug Administration under Investigational New Drug #128206. The trial was monitored by an independent data safety and monitoring board and was registered with ClinicalTrials.gov (NCT02840097). We reported results in accordance with the CONSORT extension for reporting of pilot and feasibility trials.[28]

Participants

Inclusion and exclusion criteria—Children younger than 18 years with evidence of hemorrhagic injuries to the torso and/or brain were eligible. Eligible patients were stratified into three groups based on their injuries (brain injury, torso injury, or brain and torso injury). Patients in the combined brain and torso injury group were required to meet entry criteria for both injuries. See Box 1 and 2 for specific inclusion and exclusion criteria.

Screening and consent—At participating sites' emergency departments (ED), injured children were screened by clinical research coordinators and potentially eligible patients were discussed with the treating physicians and study investigators. On arrival to the ED, eligible children had primary and secondary trauma evaluations completed by the physicians providing clinical care. All participants received diagnostic testing as deemed appropriate by the treating physicians (i.e., standard care).

Due to the narrow therapeutic time window of TXA (3 hours from the time of injury),[29] we used federal exception from informed consent (EFIC) procedures. The use of EFIC was approved after demonstrating that enrollment solely with written informed consent was not feasible (using an a priori futility threshold) during the first 3 months of the trial.[30] The futility thresholds were calculated using 95% confidence intervals around the monthly enrollment rate. If the probability of enrolling 40 patients by the end of eight months was less than 50% using the higher end of the confidence interval, the enrollment strategy would be deemed futile and we would convert to the use of EFIC study procedures. Assuming all 4 sites were enrolling patients, this futility threshold translated to 0 enrollments at 1 month, 4 enrollments or fewer at 2 months, 9 enrollments or fewer at 3 months, and 14 enrollments or fewer at 4 months. If the parent or guardian was at the bedside, and there was sufficient time, we obtained written informed consent. When the parent or guardian was not present or was unable to provide written informed consent (e.g., parent also seriously injured), or the enrollment window was closing, we enrolled the patient using EFIC procedures. If a family member (other than the parent or guardian) was present at the bedside, however, we provided them the opportunity to object to the enrollment. In this scenario, the family member was provided a brief overview of the study and an explanation on why we were unable to obtain written informed consent due to the absence of the parent or guardian and the narrow therapeutic time window. If the family member declined patient enrollment, the patient was not enrolled. If no objections were made, however, the patient was enrolled using EFIC. When a patient was enrolled using EFIC, we attempted to obtain written informed consent from the parent or guardian at the earliest opportunity after enrollment. If the parent or guardian did not want their child to participate in the trial, the patient was removed from the trial but followed for adverse events.

Interventions

We randomized children into one of three arms: 1) TXA 15 mg/kg bolus dose over 20 minutes, followed by 2 mg/kg/hr infusion over 8 hours (total dose 31 mg/kg), 2) TXA 30 mg/kg bolus dose over 20 minutes, followed by 4 mg/kg/hr infusion over 8 hours (total dose 62 mg/kg), and 3) normal saline placebo bolus over 20 minutes followed by a normal saline infusion over 8 hours.

Study patients, treating clinicians, and study team members were all blinded to study arm assignments. Blinding was provided using identical-appearing fluid, packaging, volume, and rates of infusion. Unblinding was prohibited as there is no reversal agent for TXA. Clinicians were informed to assume the patient had received TXA and treat accordingly.

The study drug was discontinued if any of the following occurred: suspected anaphylactic reaction, severe renal impairment (creatinine clearance less than 29 mL/min/1.73m^2) was identified on subsequent laboratory measurements, withdrawal of consent by the patient's parent or guardian, or discovery of new information which would make the patient ineligible to continue participation in the study.

Randomization

To rapidly complete randomization, the study intervention was pre-assigned using a central randomization process coordinated by the trial data coordinating center and the UC Davis Good Manufacturing Practice Laboratory. Prior to enrollment at each site, a study drug box containing a vial of masked study drug with a numerical identification code corresponding to the treatment assignment was designated.

Because we evaluated TXA for different injury patterns (brain injury, torso injury, or brain and torso injuries), randomization was stratified by injury group. Eligible patients were randomized into one of the three arms in a 1:1:1 ratio (TXA 15 mg/kg bolus dose, TXA 30 mg/kg bolus dose, or placebo). We performed permuted-block randomization (blocks of three) across injury group (i.e., brain, torso, or both brain and torso). A patient was considered enrolled when randomization occurred.

Outcomes

Feasibility Outcomes—We measured outcomes to assess the feasibility of the subsequent phase 3 trial. These included the enrollment rate (patients per site per month), study drug administration (percent receiving study drug), and follow-up (percent with the primary clinical outcome measured). We set an *a priori* enrollment threshold of at least 1.25 study patients per site per month using EFIC procedures. This enrollment rate would justify the feasibility of conducting a phase 3 clinical trial of 2000 patients at 30 to 40 sites over a 4-year period to detect the minimally clinically important difference of the primary outcome (4.5 units of the PedsQL). We also set a threshold on our ability to obtain the primary outcome in enrolled patients. If fewer than 75% of patients had a calculable primary outcome, then we would also not continue to the phase 3 trial or a different outcome measurement would be considered.

Prior to the start of the trial, transfusion and traumatic brain injury (TBI) guidelines were developed to standardize care across participating sites. Collaborating pediatric trauma surgeons, transfusion medicine physicians, pediatric critical care physicians, pediatric anesthesiologists, and pediatric emergency medicine physicians established general guidelines for indications and thresholds for blood product transfusion using Delphi consensus methods.[31] To measure adherence to the transfusion guidelines, site investigators reviewed all blood product transfusions and evaluated whether there were deviations from the transfusion guidelines (Appendix). In conjunction with pediatric neurosurgeons at participating sites, we also developed guidelines for the management of children with moderate and severe TBIs (Appendix). To measure adherence to the TBI guidelines, we measured the duration of time (in minutes) children with TBIs had intracranial pressures (ICP) greater than 20 mmHg.

Clinical Outcomes—Although the trial was not powered to evaluate the efficacy of clinical outcomes, we collected the following outcomes: the Pediatric Quality of Life Inventory (PedsQL; primary clinical outcome; measure of global functioning), the Pediatric Glasgow Outcome Scale - Extended (GOS-E Peds; global functioning), digit span recall (a test of working memory for children 3 years and older), total blood products (ml/kg)

transfused over the initial 48 hours of care (for children with torso injuries), intracranial hemorrhage progression in first 24 hours (for children with brain injuries), and adverse events. The PedsQL will be the primary outcome measure for the phase 3 trial and is a well-validated measure of global functioning in preverbal and verbal children.[32] The PedsQL, GOS-E Peds, and digit span recall were measured 1 week, 1 month, 3 months, and 6 months after ED presentation for all enrolled children. Blood product transfusion volume was calculated as the total mL/kg blood products received from randomization to 48 hours after randomization. Blood products included red blood cell components, platelet components, plasma components, and cryoprecipitate.

For children with TBIs, we performed non-contrast cranial computed tomography (CT) scans 24 (±6) hours after randomization to assess for intracranial hemorrhage progression (for those who had not received a second CT scan during the specified time frame as part of routine clinical care). The 24-hour CT scan was not required of those who received a neurosurgical intervention. A study neuroradiologist, blinded to clinical data, reviewed CT scans and calculated intracranial hemorrhage progression using the ABC/2 volume estimation.[33] Intracranial hemorrhage was calculated relative to the total brain volume (calculated by the XYZ/2 volume estimation).[34,35]

We evaluated for thromboses through the 7th day after randomization or at hospital discharge (whichever came first) via review of the electronic medical record. Acute thrombosis was defined as any venous or arterial thrombosis on diagnostic imaging post-randomization. Seizures, documented clinically or via electroencephalogram, occurring within the initial 24 hours of study drug administration were recorded. All study patients were followed for 180 days after randomization or until death, whichever came first, regardless of whether the patients had completed the study intervention.

Analysis

We reported patient characteristics and outcomes using descriptive statistics. As this study was a pilot trial to assess the feasibility of study procedures, the study was not powered for a particular outcome. At the recommendation of the FDA, we also conducted a sensitivity analysis evaluating the physical domain of the PedsQL alone given the possibility that the psychosocial (emotional, social, and school functioning) domains of the PedsQL are sensitive to external factors unrelated to the injury and that the physical domain alone may be a more valid measure of recovery after significant trauma.

RESULTS

Patient Characteristics

A total of 164 patients were screened, of whom 63 (38.4%) met eligibility criteria. Of patients who were eligible, 31 (49%) were enrolled. Twelve (38.7%) patients were randomized to the placebo arm, 9 (29%) to the TXA 15 mg/kg bolus arm, and 10 (32%) to the TXA 30 mg/kg bolus arm. Sixteen (52%) patients were in the brain injury group and 15 (48%) in the torso injury group, and no patients had both injuries (see eTable 1 for details of group specific inclusion criteria). Two patients were enrolled but later found to be

ineligible. Both patients had suspected cerebral sinus thromboses on initial CT angiography obtained prior to randomization but the thromboses were not identified by the radiologists until after randomization. The primary outcome (PedsQL) was collected in all eligible, enrolled patients. Details regarding screening, randomization, and follow-up of the patients are shown in the Figure.

Baseline characteristics of the study arms are described in Table 1 and eTables 2 and 3. The mean age of enrolled patients was 10.7 years (standard deviation [SD] 5.0) with a range of 0.2 to 18.0; 22 (71%) patients were male, and 16 (52%) patients were White. The mean time from injury to ED arrival was 1.0 hour (SD 0.6) and the mean time from injury to randomization was 2.4 hours (SD 0.6). The median initial Glasgow Coma Scale (GCS) score was 9 (95% CI 3 to 13) in patients in the TBI group and 15 (95% CI 9 to 15) in patients in the torso injury group. Seven (23%) patients went directly to the operating room from the ED. The mean Injury Severity Scale (ISS) score was 14.6 (SD 5.6) and the median length of hospitalization was 8 days (interquartile range of 3, 24, range of 0 to 99).

Main Results

Only one patient was enrolled prior to implementation of EFIC procedures. After the implementation of EFIC procedures, 30 patients were enrolled, with a rate of enrollment of 1.34 patients per site per month. There were 22 (71%) patients enrolled with EFIC, and none of their parents or guardians refused written informed consent when approached after randomization.

All enrolled patients (31/31, 100%) received a complete bolus and 28 of 31 (90%) received the complete 8-hour maintenance infusion. See Table 2 for protocol adherence results. One patient's intravenous catheter became dysfunctional and they were therefore unable to receive the complete maintenance infusion. The two patients later found to be ineligible due to suspected cerebral venous sinus thromboses had their maintenance study drug stopped before completion.

No differences were identified across study arms in the PedsQL, GOS-E Peds, and digit span test (Table 3 and eTables 4 and 5). In addition, no differences were identified between groups in blood product transfusion amounts or CT hemorrhage progression. One (3%) of 31 enrolled patients had a seizure within the first 7 days after randomization (placebo arm) and no patients had acute thromboses identified after randomization. No deviations from the transfusion guidelines occurred and one patient (placebo group) had an ICP over 20 mmHg for 165 minutes. The sensitivity analysis evaluating the physical domain of the PedsQL also did not demonstrate any differences between study arms (eTable 6).

DISCUSSION

We designed this pilot trial to mirror the subsequent definitive trial regarding study design, interventional arms, procedures, and outcome measures. Implementation of the study protocol allowed for assessment of critical aspects of the pilot trial including the number of eligible patients at study sites, appropriateness of the inclusion and exclusion criteria,

feasibility of timely consent and enrollment procedures, protocol adherence and variability of care, and measurement of outcomes.

We enrolled 1.34 patients per site per month using EFIC procedures, above the threshold for success needed for the definitive trial. This enrollment rate demonstrated the feasibility of a subsequent phase 3 clinical trial enrolling 2000 severely injured children over a 4-year period. The inclusion and exclusion criteria resulted in an enrolled study cohort with significant hemorrhagic injuries as noted by the high proportion of patients receiving surgical interventions, the mean ISS, and the mean length of hospitalization. Enrollment of patients that have no chance to benefit from the study intervention (i.e., too severely ill or too healthy) has a dilutional effect on the study intervention which we rigorously sought to avoid. Importantly, all eligible patients randomized received study drug and completed measurements of the primary outcome. Lack of adherence to study arm protocol and patient attrition also compromise interventional signal and trial rigor, which we did not identify in this pilot study. Although the pilot trial was not powered to assess efficacy, we collected the anticipated clinical outcomes for the subsequent phase 3 trial. The results of the pilot trial will help refine analytical plan estimates for the phase 3 trial. Finally, care appeared to be standardized across sites, with no deviations from transfusion guidelines and only one patient with a persistently elevated ICP. This was reassuring, as variability of care also may lead to a dilutional effect of the study intervention.

Because prior experience demonstrating approximately 50% of children with moderate-to-severe TBI do not have their parents or guardians present in the ED during the initial three hours after injury, we designed the trial using EFIC procedures.[36] We were advised by the Federal Drug Administration to start the trial enrolling solely with written informed consent. However, our early experience clearly demonstrated that we were unable to meet recruitment targets during the enrollment window using only written informed consent and that the use of EFIC was crucial to the feasibility of study enrollment. More than 70% of patients were enrolled using EFIC procedures, which were well-accepted by parents and guardians.

Clinical trials involving critically ill children face more challenges compared to similar trials in adults. Pediatric trials draw from a smaller patient pool and children typically have less associated morbidity and mortality compared to similar trials of adults, making it more difficult to recruit adequate numbers of patients or power for severe outcomes.[37] The need for parental consent and child assent often leads to variability in consent processes and local ethics committee reviews across sites.[37,38] These challenges have led to an inadequate number of pediatric clinical trials addressing important clinical questions.[39] Specifically for the evaluation of TXA in trauma, there are currently 10 completed or open clinical trials in adults with hemorrhagic trauma but none in children.[40]

Prior pediatric pilot studies have provided guidance about the feasibility of subsequent phase 3 trials. The Thrombolysis in Pediatric Stroke (TIPS) trial was a phase 1 trial to assess treatment with intravenous tissue plasminogen activator in children with acute ischemic stroke.[37] After 3 years of preparation, the trial was prematurely stopped due to lack of patient accrual. Only one patient was enrolled in the 17 active sites (median time active enrollment, 9 months/site). In contrast, the Therapeutic Hypothermia After

Pediatric Cardiac Arrest (THAPCA) trials conducted a pilot phase to assess the feasibility of two larger-scale trials (one for in-hospital cardiac arrest and one for out-of-hospital cardiac arrest), specifically around the feasibility of the consent process and the ability to obtain long-term follow-up in critically ill children.[41] Ultimately the 18-month pilot phase demonstrated successful recruitment (threshold attained 4 months ahead of schedule) and included four protocol amendments to augment enrollment. The full-scale THAPCA trials were subsequently approved and successfully completed.[42]

LIMITATIONS

The results of the trial should be interpreted in the context of several limitations. The results may not be generalizable to a larger number of clinical sites for the subsequent phase 3 study. However, because the pilot trial was conducted at four clinical sites, with each site bringing its own demographic, geographic, and clinical differences, we are better able to anticipate potential barriers for the subsequent trial. Prior to the start of the pilot trial we established general guidelines for blood transfusion and neurosurgical management to standardize care across clinical sites. We evaluated adherence to these guidelines using two measures. However, it will likely be more difficult to avoid variability of care across the many sites in the subsequent phase 3 trial. This will have to be closely monitored. Only 19 patients received study drug, therefore it is difficult to evaluate safety. However, there is a large body of data demonstrating the safety of TXA in children.[43] Finally, approximately half of the eligible patients were enrolled in this pilot trial. Improvement of enrollment rates of eligible patients across sites would increase the feasibility of the subsequent trial.

CONCLUSIONS

Based on the number of patients, enrollment rate, adherence to protocol, and ability to measure the primary outcome in this pilot trial, conducting a large-scale, randomized trial evaluating the efficacy of TXA in severely injured children with hemorrhagic brain and/or torso injuries is feasible. EFIC procedures were frequently used for enrollment and are essential to the feasibility of the phase 3 trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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UC Davis

Marike Zwienenberg

Joseph M. Galante

Sarah E. Barnhard

Jordan Sandhu

Leah S. Tzimentatos

Nationwide

Rachel M. Stanley

Rajan K. Thakkar

Eric A. Sribnik

Kathleen K. Nicol

Utah

Stephen J. Fenton

Doug L. Brockmeyer

Theodore J. Pysher

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Box 1. Inclusion Criteria for TIC-TOC trial

Penetrating Torso Trauma:

- Penetrating trauma to the chest, abdomen, neck, pelvis, or thigh with **at least one of the following:**
  - age-adjusted hypotension, or
  - age-adjusted tachycardia despite adequate resuscitation fluids, or
  - radiographic evidence of internal hemorrhage, or
  - clinical suspicion of ongoing internal hemorrhage

Blunt Torso Trauma:

- Clinician suspicion of hemorrhagic blunt torso injury **and at least one of the following:**
  - age-adjusted hypotension, or
  - persistent age-adjusted tachycardia despite adequate resuscitation fluids
- Hemothorax on chest tube placement or imaging; or
- Clinical suspicion of hemorrhagic blunt torso injury ***and*** intraperitoneal fluid on abdominal ultrasonography (Focused Assessment with Sonography in Trauma; FAST); or
- Intra-abdominal injury on CT with either contrast extravasation or more than trace intraperitoneal fluid; or
- Pelvic fracture with contrast extravasation ***or*** hematoma with age-adjusted tachycardia or age-adjusted hypotension on abdominal/pelvic CT scan

Head Trauma:

- GCS score 3 to 13 with associated intracranial hemorrhage on cranial CT scan

Box 2. Exclusion criteria for TIC-TOC trial (*any of the items*)

1. Unable to administer study drug within 3 hours of traumatic event
2. Known pregnancy
3. Known prisoners
4. Known wards of the state
5. Cardiac arrest prior to randomization
6. GCS score of 3 with bilateral unresponsive pupils
7. Isolated subarachnoid hemorrhage, epidural hematoma, or diffuse axonal injury
8. Known bleeding/clotting disorders
9. Known seizure disorders
10. Known history of severe renal impairment
11. Unknown time of injury
12. Previous enrollment into the TIC-TOC trial
13. Prior TXA for current injury
14. Non-English and non-Spanish speaking
15. Known venous or arterial thrombosis

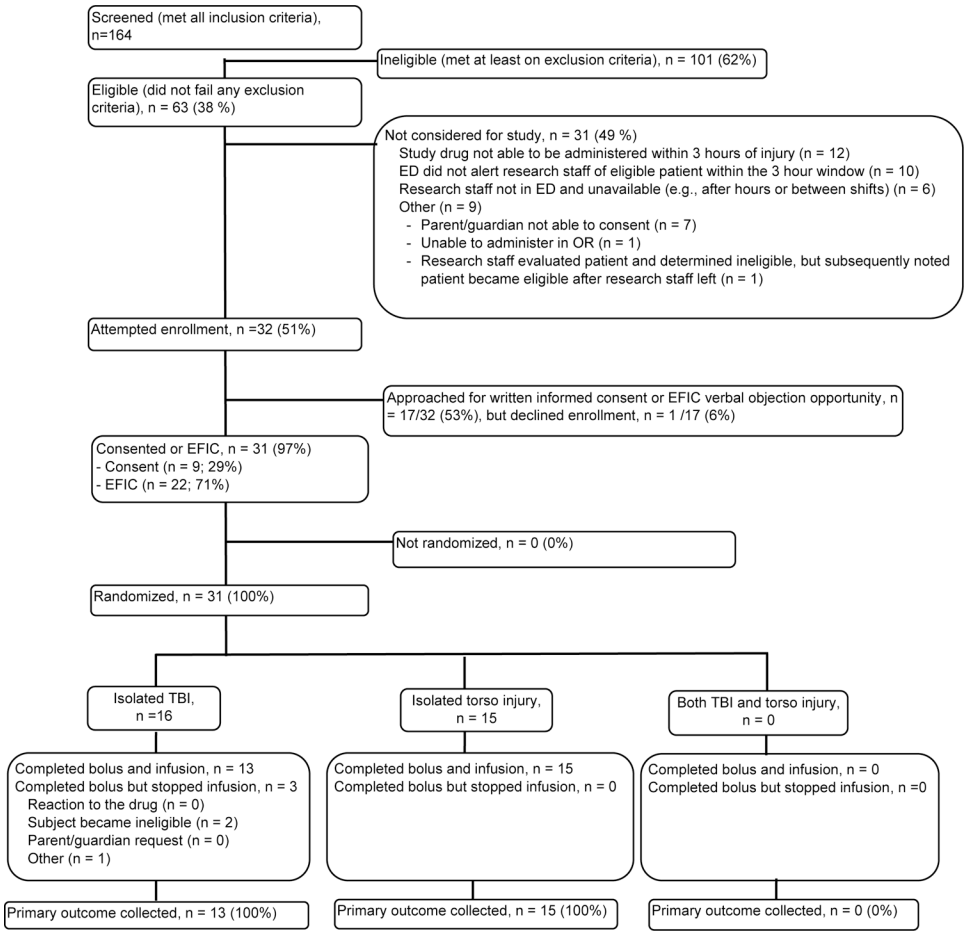

Figure.
TIC-TOC pilot trial CONSORT diagram

Table 1.

Patient characteristics by treatment group, n (%)

	Overall (n = 31)	Placebo (n = 12)	TXA 15 mg/kg (n = 9)	TXA 30 mg/kg (n = 10)
Demographics				
Age at randomization (years), mean (SD)	10.7 (5.0)	9.2 (6.1)	12.6 (4.4)	10.7 (4.0)
< 2 years	3 (10)	2 (17)	1 (11)	0 (0)
2–9 years	7 (23)	3 (25)	0 (0)	4 (40)
>= 10 years	21 (68)	7 (58)	8 (89)	6 (60)
Male	22 (71)	9 (75)	5 (56)	8 (80)
Race				
Asian	1 (3)	1 (8)	0 (0)	0 (0)
Black or African American	8 (26)	4 (33)	2 (22)	2 (20)
White	16 (52)	6 (50)	4 (44)	6 (60)
Multiple	1 (3)	0 (0)	1 (11)	0 (0)
Unknown or not reported	5 (16)	1 (8)	2 (22)	2 (20)
Injury Characteristics				
Injury group				
TBI	16 (52)	7 (58)	4 (44)	5 (50)
Torso	15 (48)	5 (42)	5 (56)	5 (50)
Method of transport to ED				
EMS air	10 (32)	5 (42)	1 (11)	4 (40)
EMS ground	17 (55)	4 (33)	8 (89)	5 (50)
Private vehicle/walk-in	1 (3)	1 (8)	0 (0)	0 (0)
Interfacility transfer	1 (3)	1 (8)	0 (0)	0 (0)
Multiple methods of transportation	2 (7)	1 (8)	0 (0)	1 (10)
Time from injury to ED arrival (hours), mean (SD)	1.0 (0.6)	1.1 (0.8)	0.8 (0.5)	1.2 (0.5)
Time from injury to randomization (hours), mean (SD)	2.4 (0.6)	2.4 (0.7)	2.3 (0.5)	2.5 (0.4)
Primary mechanism of injury				
Fall from greater than standing height	5 (16)	2 (17)	1 (11)	2 (20)
MVC	9 (29)	2 (17)	3 (33)	4 (40)
Pedestrian/bicyclist hit by moving vehicle	4 (13)	3 (25)	1 (11)	0 (0)
Gun-shot wound	4 (13)	2 (17)	2 (22)	0 (0)
Recreational vehicle injury	1 (3)	0 (0)	0 (0)	1 (10)
Sports-related injury	5 (16)	2 (17)	2 (22)	1 (10)
Other	3 (10)	1 (8)	0 (0)	2 (20)
Initial GCS total score, median [Q1, Q3]				
TBI/Both	9 [3,13]	3 [3,13]	13 [10,13]	11 [7,13]
Torso	15 [9,15]	15 [9,15]	15 [14,15]	15 [14,15]
Hypotension	2 (7)	1 (8)	0 (0)	1 (10)
Tachycardia	9 (29)	5 (42)	1 (11)	3 (30)
Temperature (Celsius), mean (SD)	36.5 (0.7)	36.4 (1.0)	36.5 (0.7)	36.7 (0.3)

	Overall (n = 31)	Placebo (n = 12)	TXA 15 mg/kg (n = 9)	TXA 30 mg/kg (n = 10)
ED disposition				
OR	7 (23)	3 (25)	3 (33)	1 (10)
Admit	24 (77)	9 (75)	6 (67)	9 (90)
Patient received craniotomy or craniectomy	3 (10)	2 (17)	0 (0)	1 (10)
Patient received an intracranial pressure monitor	4 (13)	3 (25)	0 (0)	1 (10)
Patient received a laparotomy	7 (23)	2 (17)	3 (33)	2 (20)
Patient received a thoracotomy	2 (7)	1 (8)	1 (11)	0 (0)
Length of hospitalization (days), mean (SD)	15.4 (20.2)	22.3 (28.2)	8.3 (8.0)	13.6 (14.7)
Injury Severity Scale score, mean (SD)	14.6 (5.6)	13.8 (5.7)	15.1 (5.8)	15.2 (5.7)
Presence of peritoneal free fluid on initial FAST exam	4 (13)	1 (8)	1 (11)	2 (20)
Mortality	0 (0)	0 (0)	0 (0)	0 (0)
Baseline labs				
pH, mean (SD)	7.3 (0.1)	7.3 (0.1)	7.3 (0.1)	7.3 (0.1)
Serum bicarbonate (mmol/L), mean (SD)	21.4 (2.5)	21.5 (3.2)	20.4 (2.2)	22.0 (1.7)
Creatinine (mg/dL), mean (SD)	0.7 (0.3)	0.6 (0.3)	0.7 (0.2)	0.6 (0.2)
INR, mean (SD)	1.1 (0.2)	1.2 (0.2)	1.1 (0.1)	1.1 (0.2)
Hemoglobin (g/dL), mean (SD)	12.8 (1.7)	12.5 (2.0)	13.0 (1.1)	13.1 (1.9)
Platelets (10/μL), mean (SD)	329.7 (133.6)	374.7 (138.7)	323.5 (117.9)	285.0 (136.5)
Glomerular filtration rate (beside Schwartz formula)				
Moderate renal dysfunction	1 (3)	1 (8)	0 (0)	0 (0)
Normal renal function	30 (97)	11 (92)	9 (100)	10 (100)

Abbreviations: ED, emergency department; EMS, emergency medical services; MVC, motor vehicle collision; FAST, Focused assessment with sonography for trauma; CT, computed tomography; GCS, Glasgow coma scale; INR, international normalized ratio

Table 2.

Adherence measures by treatment group, n (%)

	Overall (n = 31)	Placebo (n = 12)	TXA 15 mg/kg (n = 9)	TXA 30 mg/kg (n = 10)
Overall cohort				
Study drug administration (all patients)				
Received entire bolus infusion	31 (100)	12 (100)	9 (100)	10 (100)
Received entire maintenance infusion	28 (90)	11 (92)	8 (89)	9 (90)
Reason study drug stopped				
Patient ineligible[a]	2 (7)	0 (0)	1 (11)	1 (10)
Other[b]	1 (3)	1 (8)	0 (0)	0 (0)
TBI only				
Study drug administration				
Received entire bolus infusion	16 (100)	7 (100)	4 (100)	5 (100)
Received entire maintenance infusion	13 (81)	6 (86)	3 (75)	4 (80)
Reason study drug stopped				
Patient ineligible[a]	2 (13)	0 (0)	1 (25)	1 (20)
Other[b]	1 (6)	1 (14)	0 (0)	0 (0)
Adherence assessment				
Patient ICP over 20 mmHg during the first 48 hours (since randomization)	1 (6)	1 (14)	0 (0)	0 (0)
Time in minutes ICP was over 20 mmHg	165	165	-	-
Deviation from blood transfusion guidelines	0 (0)	0 (0)	0 (0)	0 (0)
Torso injury only				
Study drug administration				
Received entire bolus infusion	15 (100)	5 (100)	5 (100)	5 (100)
Received entire maintenance infusion	15 (100)	5 (100)	5 (100)	5 (100)

Abbreviations: ICP, intracranial pressure

[a]Both patients had suspected sinus thromboses on initial CT angiography obtained prior to randomization but the thromboses were not identified by the radiologist until after randomization.

[b]Other stop reason: IV line for study drug failed. Nursing staff could not get replaced on patient.

Table 3.

Clinical outcome measures by treatment group, mean (SD)

	Overall (n = 31)	Placebo (n = 12)	TXA 15 mg/kg (n = 9)	TXA 30 mg/kg (n = 10)
Outcome measures				
Area under the curve[a]	64.3 (17.2)	67.2 (20.0)	64.9 (19.0)	60.2 (12.3)
Total PedsQL score at 1 week	51.6 (24.3)	57.9 (28.6)	43.7 (24.0)	52.4 (20.1)
Total PedsQL score at 1 month	59.9 (22.0)	60.5 (27.9)	57.0 (19.8)	61.5 (16.9)
Total PedsQL score at 3 months	74.3 (21.2)	68.9 (22.5)	77.3 (23.6)	77.5 (18.5)
Total PedsQL score at 6 months	77.9 (21.4)	68.9 (25.9)	81.6 (23.0)	84.3 (9.9)
Peds GOS-E				
GOS-E Peds score, 1 week post-injury	5.1 (2.0)	5.3 (2.2)	4.6 (2.3)	5.2 (1.8)
GOS-E Peds score, 1 month post-injury	4.8 (1.9)	4.5 (2.2)	4.9 (2.0)	5.1 (1.4)
GOS-E Peds score, 3 months post-injury	4.2 (2.0)	4.2 (2.4)	3.8 (2.3)	4.6 (1.3)
GOS-E Peds score, 6 months post-injury	3.6 (2.3)	4.3 (2.3)	3.7 (2.6)	2.9 (2.3)
Digit span test				
Total forward digit span, 1 week	8.5 (3.1)	8.8 (2.8)	8.4 (1.7)	8.4 (4.3)
Total backward digit span, 1 week	6.3 (2.4)	7.3 (1.0)	6.0 (1.6)	6.0 (3.3)
Total forward digit span, 1 month	7.6 (2.8)	7.5 (2.6)	7.2 (1.9)	7.9 (3.7)
Total backward digit span, 1 month	5.8 (2.0)	5.3 (2.6)	6.2 (1.8)	6.2 (1.3)
Total forward digit span, 3 months	9.3 (2.7)	8.6 (2.5)	9.1 (3.6)	10.4 (1.5)
Total backward digit span, 3 months	7.7 (2.4)	6.5 (1.1)	8.7 (3.6)	7.8 (0.8)
Total forward digit span, 6 months	10.0 (3.2)	8.4 (2.3)	11.7 (3.9)	10.0 (2.4)
Total backward digit span, 6 months	7.5 (3.8)	5.8 (2.9)	10.4 (4.1)	6.0 (2.4)
Adverse events, n (%)				
Patient had a seizure during the first 7 days of their hospital stay or at discharge (whichever was first)	1 (3)	1 (8)	0 (0)	0 (0)
Acute thrombosis during the first 7 days of their hospital stay or at discharge (whichever was first)	0 (0)	0 (0)	0 (0)	0 (0)
Blood transfusion (Torso injury), mean (SD)				
Patient received a blood product transfusion, n (%)	7 (47)	3 (60)	2 (40)	2 (40)
Massive transfusion protocol initiated at any point, n (%)	2 (13)	0 (0)	1 (20)	1 (20)
Total amount of blood products transfused within 48 hours of injury (mL/kg)	6.1 (10.3)	6.5 (9.7)	4.9 (11.0)	7.0 (12.4)
RBCs transfused within 48 hours of injury (mL/kg)	3.0 (5.0)	3.9 (5.4)	0.7 (1.6)	4.4 (6.8)
FFPs transfused within 48 hours of injury (mL/kg)	2.4 (5.1)	2.6 (5.8)	2.1 (4.7)	2.6 (5.8)
Platelets transfused within 48 hours of injury (mL/kg)	0.6 (2.5)	0 (0)	1.9 (4.3)	0 (0)
Cryoprecipitate transfused within 48 hours of injury (mL/kg)	0.1 (0.2)	0 (0)	0.2 (0.4)	0 (0)
CT hemorrhage progression (TBI group)				
n	15	7	4	4
Baseline ratio of intracranial hematoma to total brain volume	0.011 (0.016)	0.018 (0.022)	0.009 (0.008)	0.001 (0.001)
Follow-up 24-hour ratio of intracranial hematoma to total brain volume	0.009 (0.020)	0.015 (0.028)	0.005 (0.007)	0.001 (0.000)

	Overall (n = 31)	Placebo (n = 12)	TXA 15 mg/kg (n = 9)	TXA 30 mg/kg (n = 10)
Ratio of ratios (24-hour ratio/ baseline ratio) of intracranial hematoma to total brain volume	0.644 (0.520)	0.570 (0.564)	0.654 (0.473)	0.765 (0.608)
Difference in intracranial hematoma to total brain volume ratios	0.002 (0.009)	0.003 (0.013)	0.003 (0.004)	0.001 (0.001)

Abbreviations: PedsQL, Pediatric quality of life inventory; GOS-E, Glasgow outcome scale - extended; RBC, red blood cells; FFP, fresh frozen plasma

[a]Area under the curve is measured by calculating the area under the curve using measurements taken at 1 week, 1 month, 3 months, and 6 months.