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Tranexamic acid as an adjunct to resuscitative endovascular balloon occlusion of the aorta does not worsen outcomes in a porcine model of hemorrhage

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ABSTRACT

Background Non-compressible torso hemorrhage (NCTH) represents a leading cause of preventable mortality in trauma. Resuscitative endovascular balloon occlusion of the aorta (REBOA) stabilizes NCTH but may predispose patients to thrombus generation. REBOA must therefore be prospectively evaluated for coagulation risks with concomitant usage of anti-fibrinolytic tranexamic acid (TXA). Using a porcine model of hemorrhage, it was hypothesized that TXA with REBOA would worsen coagulation outcomes and organ damage.

Materials and methods Thirty-two male Yorkshire swine underwent 30% blood volume hemorrhage with randomization to vehicle control (VC; normal saline), VC+REBOA, TXA, or TXA+REBOA. At T0, animals received 10 mL/minute of group-specific infusion (GSI) followed at T10 by 500 mL of whole blood (WB), second GSI at 13 mL/hour, and Zone 1 REBOA inflation in REBOA groups. At T40, REBOA was deflated, with additional 500 mL WB, and continuation of GSI for 3 hours. Physiological, coagulation, and inflammatory parameters were measured throughout the protocol, with postmortem histopathology.

Results After REBOA deflation at T40, lactate was significantly higher for the REBOA groups versus the non-REBOA groups, and pH, bicarbonate, and base excess were all significantly lower than the non-REBOA groups. There were no significant differences observed between groups in coagulation, inflammatory, metabolic, or histopathologic parameters.

Conclusions Administration of TXA with REBOA did not cause more deleterious coagulation outcomes. All significant changes were expected results of REBOA ischemia, and not attributable to TXA treatment. This suggests NCTH can safely be treated with both hemorrhage control methods without exacerbating clotting outcomes.

Level of evidence Not applicable—basic animal research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current contraindications for resuscitative endovascular balloon occlusion of the aorta (REBOA) include the administration of tranexamic acid (TXA) due to the increased risk of off-site clotting below the occlusion site; however, this has not been fully investigated.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that the use of REBOA and TXA in a hemorrhagic shock model does not negatively affect the coagulation profile or cause off-site clotting that could lead to increased mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings from this study provide evidence that could support further clinical investigations of the concomitant use of TXA and REBOA in patients with non-compressible hemorrhage.

⇒ Additionally, this work may support changes in Clinical Practice Guidelines and open the door for more patients to receive these adjuncts.

INTRODUCTION

With non-compressible junctional or truncal injuries constituting over 86% of patients, uncontrolled hemorrhage remains the leading cause of potentially survivable combat casualty mortality.[1–3] Applying the military definition of non-compressible torso hemorrhage (NCTH) to civilians, the mortality rate remains devastatingly high at 45% with the most lethal injury being major torso vascular injury.[3] Injuries causing NCTH present a challenge at all levels of care as hemorrhage control is difficult to obtain with conventional methods of pressure, balanced resuscitation, and tourniquet application. Without surgical intervention, unmitigated bleeding continues, and thus more than half of patients will present in extremis at a treatment facility.[4 5]

Resuscitative endovascular balloon occlusion of the aorta (REBOA) has become popular as a technique to achieve temporary hemodynamic stabilization in patients with NCTH until surgical care obtains definitive hemostasis.[6] Timely intervention with REBOA allows for decreased overall blood loss in addition to preserved cardiac and cerebral perfusion once the aorta is occluded. However, it requires special training, time to implement (averaging approximately 8 minutes to achieve aortic occlusion), and dedicated assets to place successfully.[7] During implementation of REBOA, bleeding is ongoing, which can ultimately be fatal.

Tranexamic acid (TXA) is an inexpensive and widely available receptor antagonist that inhibits

tissue plasminogen activator (tPa)-induced fibrinolysis by occupying the lysine binding sites on plasminogen. The effectiveness of TXA in trauma-related hemorrhage has been studied on a large scale with the CRASH-2 Trial showing a survival advantage in patients who receive TXA.[8] In the retrospective MATTERs Study of military casualties receiving TXA administration and at least one unit of packed red blood cells, it was found that the use of TXA with blood component-based resuscitation after combat injury resulted in improved measures of coagulopathy and increased survival compared with those who did not receive TXA.[9] It has also been shown that receiving TXA reduces the probability of receiving transfusion by 30%. A recent meta-analysis of more than 40,000 patients demonstrated that delayed administration of TXA is associated with a 10% increase in mortality for every 15 minutes that TXA administration is delayed.[9–11] These studies led to the protocolized use of TXA for combat casualty care and is commonplace in the civilian setting as well.[12 13]

However, there are ongoing concerns regarding increased risk of blood clots, with several recent analyses that have shown potential increased rates of thromboembolic events both in the military and civilian settings.[14 15] In the setting of REBOA, patients are predisposed to thrombus formation due to the burden of trauma alone, plus additional low blood pressure and stagnant blood flow below the balloon occlusion. The combination of TXA and REBOA and any potential additive thromboembolic risk has not been studied. The aim of this study was to investigate the combination of TXA and REBOA in a porcine model of severe (Class III) hemorrhage.[16] It was hypothesized that the use of TXA as an adjunct to REBOA would lead to worse outcomes—including thrombosis, end organ dysfunction and damage, and spinal ischemia. Secondary outcomes included systemic vital signs, coagulation function, and biochemical markers of injury.

METHODS AND MATERIALS

Ethical approval and accreditation

All procedures were performed in facilities accredited by AAALAC International, following the ARRIVE 2.0 Guidelines. Animals were randomly assigned via random number generator to different groups by descending weight, which were blinded to investigative teams. No inclusion or exclusion criteria for animals were set prior to initiation of protocol, and all animals were required to reach the T0 time point after the initiation of protocol to be included in analyses. Statistical post hoc analysis determined no animals fell beyond 2 SD from the group mean, as such no animals were excluded from data presented.

Preoperative preparation

Thirty-two naïve castrated male Yorkshire swine (*Sus scrofa domesticus*) weighing 60 kg to 80 kg, aged 4 months to 5 months were randomized by block into four treatment groups (n=8/group): vehicle control (VC; normal saline); REBOA only (REBOA); TXA only (TXA); or REBOA plus TXA (REBOA+TXA). This military relevant study used only male Yorkshire swine based on data demonstrating males exhibit more deleterious responses to traumatic hemorrhage than females and comprise the majority of battlefield injuries.[17] Findings from this study are assumed to translate to females, however a subsequent mixed-gender analysis would be needed to prove this.

Animals were preoperatively given analgesics (Buprenex 0.01 mg/kg to 0.03 mg/kg IM) and sedated with tiletamine/zolazepam (Telazol, 4 mg/kg to 8 mg/kg IM) prior to intubation. Endotracheal intubation was performed and isoflurane maintained at 1% to 3% throughout the procedure. Core body temperature was monitored via a rectal temperature probe and maintained between 36.0°C and 38.0°C, and end-tidal carbon dioxide ($EtCO_2$) was monitored continuously.

Under ultrasound guidance the right femoral artery and the jugular vein were percutaneously cannulated with 8.5Fr catheters for controlled hemorrhage and intravenous resuscitation fluid infusion, respectively. Access for the REBOA (ER-REBOA, Prytime Medical, Boerne, Texas, USA) placement was acquired with percutaneous techniques under ultrasound guidance, in the left femoral artery using a 7.5Fr catheter. The deflated REBOA was premeasured for Zone 1 placement, introduced through the catheter, and secured. Mean arterial pressure (MAP) was continuously monitored via the arterial monitoring port located at the tip of the REBOA, allowing for monitoring above the occlusion. Continuous cerebral tissue oxygenation monitoring (rSO_2) was achieved via an rSO_2 monitor (Nonin Medical SenSmart X-100) placed at the frontal-parietal suture. All animals underwent a laparotomy and 'simulated' splenectomy by isolating and clamping splenic vessels with vascular clamps to prevent autotransfusion.

Experimental adjuncts for hemorrhage control

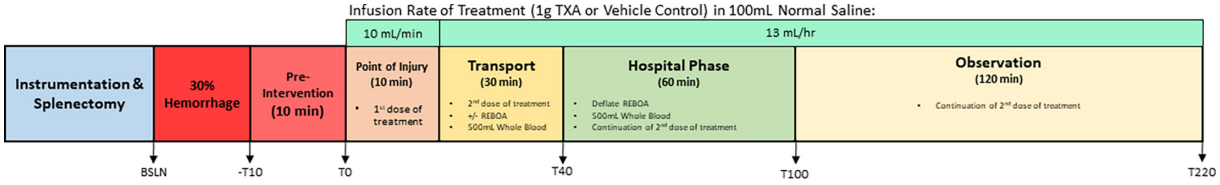
After instrumentation, the animals were allowed a 10-minute period of stabilization before baseline (BSLN) blood was drawn. Animals then underwent an ATLS Class III,[16] 30% estimated blood volume hemorrhage (19.5 mL/kg) from the right femoral artery catheter, after which a 10-minute preintervention phase was initiated (−T10).[18] Blood donor bags prefilled with 50 mL of citrate phosphate dextrose adenine (CPDA) solution were used to collect the hemorrhaged blood for subsequent resuscitation. The 10-minute preintervention period was designed to simulate a period at the point of injury without the immediate availability of medical care.

At the end of preintervention, the groups received their designated point of injury treatments (T0) of either 1 g TXA reconstituted in 100 mL normal saline per manufacturer's instruction or 100 mL of normal saline (VC) infused at a rate of 10 mL/minute. At the end of infusion (T10), a 30-minute simulated transport phase was initiated, and all animals received a 500 mL whole blood (WB) bolus, simultaneously receiving either a second 1 g TXA dose or VC at a rate of 13 mL/hour. All WB boluses were preceded by 2.5 mL of calcium gluconate (23% solution; Vedco, Saint Joseph, Missouri, USA) to counteract the effects of the CPDA. Animals in the REBOA groups had the REBOA inflated at Zone 1 immediately prior to the administration of the WB bolus.

At the beginning of the simulated hospital phase (T40), REBOA was deflated in the REBOA groups, and a second 500 mL WB bolus was administered. Designated treatments of TXA or VC continued to be infused at 13 mL/hour for the remainder of the protocol. At T100, the animals were observed for 2 hours followed by final blood draws, cerebrospinal fluid (CSF) collection, and humane euthanasia at T220. Proper REBOA placement was confirmed post mortem via thoracotomy and manual palpation of the inflated balloon. The experimental timeline is represented in figure 1.

Laboratory analysis

Blood samples were collected from the right femoral arterial line at various time points throughout the study: BSLN, end of hypovolemia (T0), end of transport (T40), end of hospital (T100),



Group Specific Intervention	Normal Saline (10mL/min)	TXA (1g in 100mL Normal Saline; 10mL/min)	Normal Saline (13mL/hr)	TXA (1g in 100mL Normal Saline; 13mL/hr)	REBOA Inflation	500mL Whole Blood
	T0		T10			
Vehicle Control	X		X			X
REBOA Only	X		X		X	X
TXA Only		X		X		X
REBOA+TXA		X		X	X	X

Figure 1 Experimental timeline. Schematic depicting experimental timeline, with time points running from instrumentation through hemorrhage, transport, hospital care, and observation. Blood draws were obtained at the following time points for labs (arterial blood gas, complete blood counts, complete metabolic panel, ROTEM, STAGO, and enzyme-linked immunosorbent assays) at baseline (BSLN), end of shock (T0), end of transport (T40), end of hospital (T100), and final (T220). No blood samples were collected at end of hemorrhage (−T10). REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid

and final (T220). WB samples were collected for arterial blood gas analysis (GEM 4000 Premier, Instrumentation Laboratory, Lexington, Massachusetts, USA), thromboelastometry analysis (ROTEM), plasma coagulation (STAGO STA Compact; Diagnostica Stago, Parsippany, New Jersey, USA), complete metabolic panel (Catalyst DX Chemistry Analyzer, IDEXX Laboratories, Westbrook, Maine, USA) and complete blood cell counts (Procyte Dx Hematology Analyzer, IDEXX Laboratories). EDTA plasma and CSF were analyzed for cytokines and chemokines via a 9-Plex Porcine ProcartaPlex (ThermoFisher Scientific, Waltham, Massachusetts, USA). Serum was analyzed for protein expression of the endotheliopathy markers syndecan-1 (BlueGene Biotech, Shanghai, China) and heparan sulfate (MyBioSource, San Diego, California, USA) via enzyme-linked immunosorbent assays.

Pathology

After euthanasia, gross examination and histopathologic scoring of each subject was performed by a board-certified veterinary pathologist blinded to treatment groups. Gross necropsy evaluated for evidence of inflammatory disease/injury, vascular injury, thrombi, hypoxic injury, shock, and general disease processes in the heart, lungs, liver, kidney, ileum, and lumbar spinal cord. H&E staining was performed for the liver, kidney, ileum, lumbar spinal cord, and right cranial and caudal lung lobes to evaluate for signs of edema, congestion, inflammation, or any tissue-specific pathologic results. Findings were scored for injury severity as 0 (normal), 1 (minimal), 2 (mild), 3 (moderate), or 4 (severe).

Statistical analysis

Prior to the beginning of the study, a statistical power analysis (G*Power V.3.1, Universitat Dusseldorf, Dusseldorf, Germany) was performed for sample size estimation based on hemorrhagic shock data from a previous study using REBOA in a porcine hemorrhage model with approximately 25% blood loss.[19] Comparing the pH in each group at 30 minutes after REBOA intervention or treatment, with an SD=0.09, estimated difference =0.17, α=0.05, and power =0.80, the resulting sample size was n=5 per group. Comparing alanine aminotransferase (ALT) with SD=11.25, estimated difference =18.62, α=0.05, and power=0.80, the sample size was n=6 per group. Therefore to allow for attrition and other mediating factors, the sample size for this study was set at n=8 in each group. Although the original article did not have significant changes in coagulation factors, other publications evaluating REBOA and coagulation have used group sizes in this range to detect significant changes in coagulation function.[20 21] All animals survived to the T0 time point and were included in study analysis. Statistical analyses were performed using Prism V.9 (GraphPad Software, La Jolla, California, USA). Data are presented as mean±SD. Multiple time-point outcomes were analyzed using two-way repeated measures analysis of variance with Bonferroni correction post hoc analysis and mixed-effects analysis with Dunnett and Sidak post hoc analyses. Histological assessment scores were analyzed via the Kruskal-Wallis test with Dunn's multiple comparisons post hoc test. Statistical significance was set at $p<0.05$.

RESULTS

Vitals and blood gas analysis

After hemorrhage, MAP decreased significantly from BSLN at hypovolemia (−T10) for all experimental groups, increased at T15 for REBOA groups, and was able to normalize by T100 for all experimental groups (table 1). Heart rate increased significantly during hypovolemia in all experimental groups and did not return to BSLN throughout the remainder of the experiment (table 1). $EtCO_2$ significantly decreased at −T10, but normalized at T0. In REBOA groups, $EtCO_2$ increased significantly at T40 on balloon deflation, and stabilized by T100 (table 1). rSO_2 was significantly higher in the REBOA groups at T15 compared with the BSLN and non-REBOA groups until deflation at T40 (table 1).

The REBOA groups showed significantly different responses as compared with the non-REBOA groups (VC and TXA) in several blood gas parameters (table 2). Whereas pH was significantly lower than BSLN at T40 for all groups, the REBOA groups were also significantly lower than the non-REBOA groups. Lactate and partial pressure of CO_2 (pCO_2) were significantly higher, and base excess (BE) and bicarbonate (HCO_3) were significantly lower from BSLN at T40 in the REBOA and REBOA+TXA groups on balloon deflation. pH, lactate BE, and HCO_3 all resolved by T220 for both the REBOA experimental groups, whereas for the non-REBOA experimental groups, these blood gas parameters resolved by T100.

Table 1 Vitals

	Vehicle control[1]	REBOA[2]	TXA[3]	REBOA+TXA[4]
	n=8	n=8	n=8	n=8
Mean arterial pressure (mm Hg)				
BSLN	62.0±15.8	60.5±16.8	63.1±8.8	69.8±15.0
–T10	*29.3±12.3*	*27.5±4.2*	*27.0±6.0*	*25.0±4.0*
T0	*38.4±12.8*	*33.5±8.6*	*37.0±11.7*	*31.4±5.3*
T10	*39.7±12.1*	*38.4±8.8*	*38.9±8.9*	*38.3±5.0*
T15	56.4±10.0[2 4]	*142.1±22.61*[1 3]	54.5±9.1[2 4]	*155.5±13.31*[1 3]
T40	56.9±5.2	52.0±22.8	55.3±8.8	*52.1±12.0*
T100	64.1±10.5	63.1±8.81	66.0±10.3	62.3±14.0
T160	69.0±14.2	66.4±8.9	68.0±10.7	62.6±9.4
T220	60.9±13.3	64.8±8.9	70.5±13.1	63.4±6.7
Heart rate (BPM)				
BSLN	88.4±19.7	91.1±23.3	79.4±21.7	78.3±14.7
–T10	120.4±12.7	*132.0±30.5*	*147.3±25.0*	*119.5±11.4*
T0	*149.9±26.8*	*146.5±32.7*	*161.7±25.5*	*132.6±16.1*
T10	*137.8±18.0*	*146.9±29.9*	*158.9±23.2*	*138.4±18.6*
T15	120.6±26.7	*133.3±33.7*	*125.6±21.2*	*144.8±38.0*
T40	*136.9±27.6*[2]	*180.9±10.61*[1 3]	*121.9±25.22*[2 4]	*166.6±29.4*[3]
T100	*155.6±30.2*	*170.1±27.03*[3 4]	*122.8±25.0*[2]	*33.6±18.8*[2]
T160	*171.8±28.0*	*180.9±27.6*	*155.5±26.5*	*156.0±21.7*
T220	*169.3±30.4*	*175.6±28.7*	*163.6±31.8*	*161.9±31.8*
$EtCO_2$ (mm Hg)				
BSLN	40.3±3.0	39.4±2.9	38.6±1.3	39.0±1.7
–T10	*30.1±7.0*	*31.3±3.4*	*28.8±4.1*	*28.1±5.3*
T0	37.0±5.5	36.5±3.3	36.4±6.5	34.5±4.5
T10	37.5±4.9	39.6±1.6	37.4±3.6	38.9±2.7
T15	42.4±2.2	42.9±3.6	41.4±3.1	39.6±7.0
T40	41.9±2.6[2 4]	*50.3±4.41*[1 3]	40.4±2.3[2 4]	*47.3±6.41*[1 3]
T100	41.8±6.6	40.4±1.5	42.3±5.1	39.9±1.8
T160	40.1±5.3	40.9±1.9	41.1±3.8	40.5±2.1
T220	38.8±4.0	40.8±1.5	42.1±3.5	39.8±3.1
rSO_2 (%)				
BSLN	53.0±7.5	59.4±7.9	57.7±9.0	57.9±6.4
–T10	47.2±8.5	54.4±5.9	52.0±11.6	50.0±5.1
T0	50.7±8.8	57.3±7.5	55.2±11.4	52.4±5.6
T10	48.2±5.6[2]	60.3±8.9[1]	54.6±10.1	53.6±6.2
T15	54.3±6.0[2 4]	*71.0±8.71*[1 3]	57.1±8.8[2 4]	*68.7±9.61*[1 3]
T40	57.7±4.4	60.3±5.9	61.9±7.5	58.3±9.1
T100	62.4±2.6	*72.5±6.5*[4]	61.2±5.7	59.4±5.0[2]
T160	*63.7±3.5*	*72.7±7.2*	66.2±5.4	63.2±6.0
T220	*63.7±4.5*	*70.3±6.3*	64.8±8.0	63.4±7.8

Results are presented as mean±SD. Statistical significance is achieved by a value of $p<0.05$. Values significantly different from BSLN are denoted in italics. Superscript numbers indicate value is significantly different from the corresponding column listed.
BSLN, baseline; $EtCO_2$, end-tidal carbon dioxide; REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid.

Organ dysfunction and damage

For complete metabolic panel (online supplemental file 1; SDC1), kidney function was assessed via blood urea nitrogen (BUN) and creatinine (CREA), showing BUN was significantly different from BSLN at T100 for the non-REBOA groups and the REBOA+TXA group, whereas at T220 all experimental groups were significantly higher than BSLN. CREA became significantly higher than BSLN in all groups at T0, and gradually increased during subsequent time points. Liver damage, assessed via ALT and aspartate aminotransferase demonstrated no significant elevations in any group compared with BSLN throughout the protocol. Pancreatic insult, assessed via amylase (AMYL) and lipase (LIPA), demonstrated no significant changes in AMYL other than a decrease at T0 that was only significant in the REBOA+TXA group whereas LIPA was significantly higher from BSLN in all experimental groups at T0 and did not return to BSLN parameters throughout the experimental timeline; additionally, the REBOA groups were significantly higher than the non-REBOA groups at T40 and remained higher, though not significantly, through T220.

Gross necropsy identified no evidence of thrombus formation or disseminated coagulopathy in any of the groups. Six tissues were scored for histology (Table 3; tissues from two animals in the VC group were unable to be obtained). Although 2 of the 18 tissue scores showed significant differences between groups, these were not identified as having changed due to treatment. All

Table 2 Arterial blood gas parameters

	Vehicle control[1]	REBOA[2]	TXA[3]	REBOA+TXA[4]
	n=8	n=8	n=8	n=8
pH				
BSLN	7.49±0.04	7.50±0.04	7.51±0.02	7.50±0.03
T0	7.46±0.06	7.46±0.03	*7.46±0.03*	*7.46±0.04*
T40	*7.43±0.062*[2 4]	*7.21±0.071*[1 3]	*7.46±0.032*[2 4]	*7.21±0.061*[1 3]
T100	7.45±0.07	*7.40±0.04*[3]	7.50±0.03[2 4]	*7.40±0.05*[3]
T220	7.50±0.06	7.47±0.05	7.52±0.03	7.49±0.06
Lactate (mmol/L)				
BSLN	2.6±1.1	2.1±0.4	2.0±0.9	1.9±0.5
T0	*3.7±1.1*	*3.3±0.8*	*3.2±0.9*	*3.6±1.1*
T40	4.9±2.0[2 4]	*10.5±1.41*[1 3]	*3.5±0.82*[2 4]	*10.5±1.21*[1 3]
T100	5.4±3.4	*7.8±1.6*[3]	2.9±1.1[2 4]	*8.6±2.2*[3]
T220	3.8±2.5	3.7±1.7[3]	1.6±0.6[2]	5.0±3.2
pCO_2 (mm Hg)				
BSLN	42.3±3.9	41.4±3.1	42.0±1.2	42.4±2.9
T0	41.9±4.4	40.9±3.1	43.4±3.4	41.1±4.8
T40	44.6±1.9	*59.3±6.3*	45.5±3.1	*60.6±10.6*
T100	43.1±6.0	42.4±2.1	44.3±4.3	42.5±2.2
T220	42.6±3.9	43.6±1.5	44.1±4.5	41.4±3.1
pO_2 (mm Hg)				
BSLN	112.0±17.0	114.5±21.6	108.9±10.3	113.6±30.8
T0	116.6±24.3	127.5±14.4	113.0±15.7	125.1±38.6
T40	97.6±9.3	92.0±23.3	106.8±10.4	90.4±25.5
T100	107.8±20.9	103.4±15.0	104.4±19.4	100.0±26.1
T220	112.6±11.9	98.3±12.0	97.8±6.5	89.5±21.6
Base excess (mmol/L)				
BSLN	8.0±3.9	8.1±1.8	9.5±1.7	9.1±1.7
T0	*5.0±3.9*	*4.9±2.2*	*6.6±1.5*	*5.0±2.0*
T40	4.8±4.3[2 4]	*−5.2±2.41*[1 3]	7.8±1.7[2 4]	*−4.5±2.31*[1 3]
T100	5.9±5.2	*1.6±2.4*[3]	10.3±1.8[2 4]	*1.7±3.1*[3]
T220	8.9±4.8	7.6±3.6[3]	*12.3±1.7*[2]	7.4±4.5
HCO_3 (mmol/L)				
BSLN	32.0±4.0	32.3±1.3	33.4±1.7	33.2±1.4
T0	*29.6±3.5*	*29.1±2.6*	*31.1±1.6*	*29.3±2.2*
T40	29.5±4.6[2]	*23.8±1.71*[1 3]	32.5±1.8[2 4]	*24.1±2.4*[3]
T100	30.3±5.2	*26.8±1.9*[3]	34.7±2.0[2 4]	*26.9±2.5*[3]
T220	32.6±4.7	32.5±2.9[3]	*36.5±2.3*[2]	31.5±4.1

Results are presented as mean±SD. Statistical significance is achieved by a value of p<0.05. Values significantly different from BSLN are denoted in italics. Superscript numbers indicate value is significantly different from the corresponding column listed.
BSLN, baseline; REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid.

findings were consistent with those expected from surgical prep and hypovolemia.

Complete blood count and inflammation

Additionally, no significant differences were seen in the leukocytes between groups, however all groups saw significant increases from BSLN by the end of the protocol (SDC2). In the VC and TXA groups, neutrophil counts were significantly elevated from BSLN at the end of transport (T40), whereas this increase was not seen in the REBOA groups until T100. By T220, in all groups, lymphocyte counts were significantly decreased from BSLN.

Interleukin (IL)-12p40 plasma levels were elevated in the REBOA+TXA group at T0 (653.04±147.93 pg/mL), T40 (1016.30±174.01 pg/mL), and T220 (636.47±119.86 pg/mL) compared with BSLN values (408.84±101.91 pg/mL) and were significantly higher at T0 compared with all treatment groups (VC: 268.43±160.85 pg/mL; REBOA: 337.91±121.60 pg/mL; TXA: 261.62±107.08 pg/mL). Across plasma and CSF, no significant differences were seen in any of the other inflammatory markers, or in serum levels of syndecan-1 and heparan sulfate.

Coagulation function

No significant differences were seen in the platelets throughout the protocol (SDC2). There were no clinically significant changes from treatment throughout any of the experimental groups for the ROTEM analysis other than significant decreases in ExTEM Maximum Lysis (ML) at T40 in both the REBOA groups (Table 4).

No clinically significant within-group or between-group differences were seen in prothrombin time, D-Dimer, and activated partial thromboplastin time (Table 5). At T0, fibrinogen was significantly decreased in all groups. This decrease was resolved by T40 in each group except the TXA only group, which did not resolve until T100. In all groups, von Willebrand factor was significantly increased at T40 and continued to increase through the remainder of the protocol. Antithrombin III was significantly decreased in all groups at T0 through T40, but resolved in all groups by T220.

DISCUSSION

NCTH presents a difficult challenge for treatment and as such, contributes to a large number of potentially survivable deaths in both military and civilian settings. Although REBOA provides a means for temporarily managing this trauma, its use alongside TXA to mitigate continued bleeding has yet to be prospectively studied. In this study, we investigated the concomitant use of TXA with REBOA in the setting of ATLS Class III hemorrhage, and found no signs of worse outcomes in coagulation, spinal ischemia, or end organ damage. Therefore, contrary to the hypothesis tested, there was no apparent 'additive' effect of thromboembolic events within the first few hours after combined use of TXA and REBOA, and lends support to the safety of concomitant use in hemorrhage resuscitation.

As expected, REBOA helped to stabilize the subject hemodynamically after deployment as evidenced by increases in MAP, heart rate, and rSO_2 at T15, and this effect remained through the simulated 'pre-hospital' period (until comprehensive resuscitation was available).

Additionally, to our knowledge, this is the first evidence for the use of non-invasive cerebral oxygen monitoring in REBOA hemorrhage resuscitation. Previous work with rSO_2 monitoring has shown promise as an adjunct to optimize resuscitation with REBOA in cardiac arrest and traumatic arrest with CPR.[22] It is understood from animal models that REBOA can increase perfusion pressure and partial pressure of oxygen to the brain above the balloon.[20 23] In this study, after balloon inflation, it appears that REBOA improves and preserves oxygen delivery to the brain, thereby theoretically protecting cerebral tissue from ischemia during hypovolemia. Comparatively, $EtCO_2$, commonly applied to indicate adequate cardiac output or return of spontaneous circulation, did not function as a measure of cerebral perfusion after balloon inflation.

There were no other significant differences in vital signs with the combined use of TXA and REBOA.

The effects of REBOA on biochemical measures is well described to include increased lactate and decreased pH, which resolve after resuscitation.[19 24] The responses seen in the arterial blood gas parameters of both the REBOA groups are consistent

Table 3 Histological scores

	Vehicle control[1]	REBOA[2]	TXA[3]	REBOA+TXA[4]	P value
	n=6	n=8	n=8	n=8	
Lung, cranial lobe					
Alveolar edema	1.5±1.1	2.1±0.4	1.9±1.0	1.6±1.1	0.5560
Congestion (capillary hypercellularity)	1.8±0.8	2.1±0.4	2.0±0.8	1.6±1.1	0.6435
Inflammation (lymphoplasmacytic infiltrates)	0.3±0.8	0.0±0.0	0.0±0.0	0.4±1.1	0.4901
Lung, caudal lobe					
Alveolar edema	2.2±0.4	**2.8±0.5[4]**	2.3±0.5	**1.8±0.9[2]**	**0.0259**
Congestion (capillary hypercellularity)	1.8±1.0	2.8±0.5	2.3±0.5	2.0±0.5	**0.0334**
Inflammation (lymphoplasmacytic infiltrates)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Liver					
Congestion (sinusoidal/venous)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Hemorrhage (acute multifocal)	0.0±0.0	0.4±1.1	0.3±0.7	0.4±1.1	0.8465
Inflammation (hepatitis, lymphoplasmacytic infiltration)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Kidney					
Congestion	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Hemorrhage (interstitial)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Inflammation (nephritis, lymphoplasmacytic infiltration)	0.5±0.8	1.4±1.3	0.5±0.9	0.6±1.1	0.3620
Ileum					
Congestion	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Hemorrhage	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Inflammation (enteritis, eosinophilic infiltration)	1.5±1.4	1.0±1.1	1.5±1.2	1.9±1.3	0.4970
Lumbar spinal cord					
Ventral horn necrosis	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	>0.9999
Perivascular microhemorrhage	0.0±0.0	0.0±0.0	0.0±0.0	0.1±0.4	0.4318
Meningeal/parenchymal congestion	0.0±0.0	0.0±0.0	0.0±0.0	0.1±0.4	0.4318

Results are presented as mean±SD. Statistical significance is achieved by value of $p<0.05$. Values with significance are denoted in bold. Superscript numbers indicate value is significantly different from the corresponding column listed.
REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid.

with previously published work from this group and others.[23] REBOA groups also induced an earlier rise in LIPA compared with the non-REBOA groups, indicative of potential pancreatic dysfunction. As no significant differences were seen between the two REBOA groups, which were significantly different from both the VC and the TXA groups, and in consideration of historical data, it is reasonable to conclude that the addition of TXA did not worsen outcomes. For all groups, BUN and CREA, markers of kidney dysfunction, became elevated, along with histopathologic evidence of nephritis. Minimal to mild levels of histopathologic enteritis, and alveolar edema with capillary hypercellularity were also detected in all groups. Furthermore, no significant evidence of spinal cord damage was identified, nor were CSF levels of inflammatory cytokines elevated. A recent porcine model of ATLS Class IV hemorrhagic shock, with Zone 1 occlusion for 90 minutes also demonstrated unremarkable histopathology in the spinal cord.[23] Therefore, as these findings were observed across all groups, there is no evidence of significant complications imparted by REBOA, TXA, or their combined use for rapid control of ATLS Class III hemorrhage.

As an antifibrinolytic drug, TXA affects coagulation to improve survival after traumatic bleeding. In the presence of severe bleeding, it reduces mortality in those that develop hyperfibrinolysis without having deleterious effects in patients that may not develop this outcome and fully benefit from administration of TXA.[25] In this animal study, the administration of TXA with subsequent REBOA deployment did not lead to worse outcomes in ROTEM and Stago-assessed coagulation function measures. There were also no thromboembolic events detected in any animals during gross necropsy or in tissue histopathology. Though short model timelines may limit conclusions about macrovascular clotting, the absence of early microvascular thrombi on histopathology is reassuring. Taken together with the TXA or the REBOA alone groups, there is no indication of deleterious effects from combined treatments.

Interestingly, although not significant between groups, and independent of TXA administration, the REBOA groups demonstrated a delay in the significant rise of circulating neutrophils, which eventually matched the non-REBOA groups after deflation and continuous observation to T220. Conversely, lymphocyte counts decreased equivalently across all groups. Other than IL-12p40 for the REBOA+TXA group, serum levels of circulating cytokines displayed no significant differences over time or between groups. This elevation in IL-12p40 was detected at T0, prior to intervention, and is therefore not attributable to therapeutic techniques. Whether this delay in neutrophil rise was attributed to a change in injury severity imparted by REBOA, or delayed by anatomic compartmentalization is out of the scope of this study and warrants further study.

TXA has gained favor as an antifibrinolytic drug to control hemorrhage and reduce mortality in not only patients who had transplants (CRASH-2), but also in patients with peripartum hemorrhage (WOMAN).[26] Concomitant TXA with REBOA for hemorrhage control in patients with placenta accreta spectrum has been explored, as multiple studies have demonstrated that aortic occlusion results in a significant reduction of maternal hemorrhage volume. Despite the reduction of blood loss from trauma or peripartum hemorrhage, when TXA is combined with aortic balloon occlusion, there have been reports of arterial-access related limb ischemic complications (ARLICs), defined

Table 4 ROTEM parameters

	Vehicle control[1]	REBOA[2]	TXA[3]	REBOA+TXA[4]
	n=8	n=8	n=8	n=8
ExTEM Clot Time (seconds)				
BSLN	49.0±4.2	46.5±2.8	49.4±3.1	49.4±3.8
T0	48.9±5.6	45.3±3.0	49.6±5.2	45.9±5.1
T40	50.8±4.2	47.8±3.0	49.8±4.3	48.0±4.8
T100	49.6±2.5	47.6±2.4	51.1±6.1	48.9±9.3
T220	52.1±5.3	47.6±2.9	49.4±7.3	48.5±5.7
ExTEM A10 (mm)				
BSLN	67.3±5.8	72.4±3.3	70.5±5.9	68.1±4.7
T0	68.0±3.1	70.4±4.0	69.1±3.5	65.6±6.8
T40	68.1±4.1	71.8±3.3	68.6±4.3	68.9±4.5
T100	66.3±5.3	71.1±2.3	67.3±6.9	68.1±5.4
T220	68.5±5.2	71.4±2.8	67.3±7.5	65.8±6.9
ExTEM Clot Formation Time (seconds)				
BSLN	53.1±14.3	42.1±4.1	46.1±11.4	48.3±9.4
T0	46.6±3.2	46.8±3.9	48.0±7.8	55.3±14.4
T40	49.8±9.6	45.6±3.5	50.8±10.5	49.6±10.9
T100	53.3±9.3	47.0±1.3	54.0±12.0	53.6±13.2
T220	49.1±9.7	46.6±2.5	55.5±20.2	56.8±14.6
ExTEM Maximum Clot Firmness (mm)				
BSLN	69.9±5.3	74.1±3.0	72.4±5.6	70.5±4.2
T0	70.3±2.4	72.5±3.8	71.5±3.0	68.4±6.2
T40	70.6±4.0	74.0±2.9	70.6±4.1	71.4±4.0
T100	69.1±4.5	73.5±2.5	69.5±6.8	70.9±4.8
T220	71.3±4.8	73.9±2.5	70.1±5.9	68.9±6.3
ExTEM α-angle				
BSLN	79.4±3.0	81.6±0.9	80.9±2.4	80.4±2.0
T0	80.6±0.8	80.9±1.1	80.6±1.4	78.9±3.1
T40	80.1±2.0	81.1±1.0	80.0±2.0	80.0±2.3
T100	79.4±2.0	80.6±0.5	79.3±2.6	79.3±2.8
T220	80.4±2.1	80.9±0.6	78.9±3.9	78.8±3.1
ExTEM Lysis Index 30 (%)				
BSLN	98.8±1.0	98.5±0.8	98.0±0.9	98.9±1.3
T0	98.4±1.7	98.5±0.5	98.0±1.1	98.9±1.4
T40	98.9±1.0	*99.5±0.8*	98.5±0.9	*99.5±1.4*
T100	99.3±0.7	99.0±0.5	*98.9±0.8*	99.1±1.4
T220	99.5±0.8	*99.3±0.7*	98.9±0.8	*99.5±1.4*
ExTEM Maximum Lysis (%)				
BSLN	10.0±4.1	11.9±2.2	12.3±3.0	11.8±3.5
T0	10.1±4.0	12.0±2.4	13.3±2.4	11.6±3.9
T40	9.8±3.2	*8.7±3.3*	13.1±3.0	*9.4±3.8*
T100	9.8±3.4	10.9±2.6	12.5±2.2	11.0±4.3
T220	8.6±3.9	*9.9±2.4*	12.0±2.6	10.9±4.0
FibTEM A10				
BSLN	25.9±7.0	31.5±2.8	30.4±5.4	28.4±6.5
T0	27.6±6.7	31.1±3.4	35.3±11.5	30.6±6.2
T40	24.9±5.4	30.1±4.2	33.4±7.8	28.6±7.7
T100	25.5±7.2	25.9±5.4	29.0±8.1	28.3±8.5
T220	25.0±5.2	30.0±5.2	31.5±7.1	28.5±9.2
FibTEM Maximum Clot Firmness (mm)				
BSLN	26.6±7.9	32.1±3.0	31.3±5.9	29.1±6.5
T0	28.3±7.1	31.8±3.7	36.9±12.2	31.5±7.0
T40	25.8±6.2	31.1±4.6	31.1±8.5	29.5±7.7
T100	27.6±8.6	26.9±6.4	31.0±8.1	30.0±8.9
T220	27.1±6.5	33.0±7.0	34.6±8.0	31.6±9.9

Results are presented as mean±SD. Statistical significance is achieved by a value of p<0.05. Values significantly different from BSLN are denoted in italics.
BSLN, baseline; REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid.

as extremity ischemia and distal embolism, at a rate of 8.6% of 418 REBOA patients, within the first two postoperative days.[27–29] Although they have no significant impact on in-hospital mortality, REBOA patients who develop these ARLICs do have a significantly higher length of stay in-hospital (seven additional days), and occasionally require embolectomy/thrombectomy or in some patients, amputation. This led to the conclusion of TXA being identified as an independent risk factor for REBOA-related ARLICs. However, this study did not include comparison to patients with ARLIC and TXA use in non-REBOA patients.[29] Comparatively, one study of Level I and II trauma centers in the USA demonstrated that in 887 trauma patients receiving TXA, similar frequencies of venous thromboembolism (VTE) occurred at 9.7%, with deep vein thrombosis and pulmonary embolism also occurring at rates of 7.8% and 3.5%, respectively.[30] It therefore stands to reason that TXA itself is related to this increase in ARLICs, independent of the presence of REBOA.[14]

Meta-analysis of combat casualty TXA use and VTE frequency, which includes the results of the CRASH-2 and MATTERs studies, among others, indicated TXA use resulted in a twofold increase of VTE frequency, and a 20-fold increase of VTE frequency in combat casualties versus civilians.[31] Despite this, the meta-analysis determined that to date, the MATTERs Study was the only sufficiently powered military trauma study to detect survival benefit, where despite increased VTE frequency, TXA use was more importantly associated with a sevenfold survival benefit in patients who also received blood products. The authors of the meta-analysis conclude along with the MATTERs Study, that VTE becomes a problem of survivorship and can be managed with appropriate VTE prophylaxis.

Limitations

Though swine are a commonly used large animal model for REBOA,[19 24 32 33] all animal models have their limitations. Although physiologically similar to humans in several areas, the porcine coagulation profile is comparatively hypercoagulable. Specifically, work with TXA in porcine hemorrhage modeling has demonstrated humans are 30 times more sensitive to tPa-induced fibrinolysis than swine.[34] Regardless of this natural resistance, TXA was still able to provide further therapeutic resistance to tPa-induced fibrinolysis in the context of porcine hemorrhage modeling. Therefore, although not always optimal for coagulation disorder studies, the combined use of TXA in a fibrinolysis-resistant porcine hemorrhage model, paired with REBOA, as used here, should be capable of producing the prothrombotic conditions for the hypothesis being tested. Despite this, the development of off-site clotting was not demonstrated throughout the vasculature or organs, nor did coagulation function parameters indicate higher risk of thrombus formation. Additionally, this model was not designed to specifically induce a hemorrhage or injury that would create hyperfibrinolysis, but rather to address if the combined use of TXA

Table 5 STAGO

	Vehicle control[1]	REBOA[2]	TXA[3]	REBOA+TXA[4]
	n=8	n=8	n=8	n=8
Prothrombin time (seconds)				
BSLN	13.3±0.6	13.2±0.5	13.1±0.4	13.5±0.6
T0	13.2±0.5	13.1±0.4	13.2±0.4	13.6±0.4
T40	13.2±0.4	13.2±0.4	13.1±0.4	13.5±0.5
T100	13.3±0.5	12.7±0.4	12.9±0.3	13.2±0.4
T220	13.0±0.4	13.0±0.4	13.0±0.5	13.2±0.3
D-Dimer (µg/mL)				
BSLN	0.7±0.3	0.5±0.1	0.5±0.3	0.6±0.02
T0	0.6±0.1	0.4±0.1	0.6±0.2	0.7±0.6
T40	0.5±0.4	0.5±0.4	0.5±0.2	0.7±0.3
T100	0.6±0.4	0.5±0.2	0.7±0.4	0.8±0.6
T220	0.7±0.3	0.5±0.3	0.5±0.4	0.6±0.3
Fibrinogen (mg/dL)				
BSLN	173.3±37.6	190.5±28.6	199.0±34.5	169.0±15.8
T0	*155.5±31.5*	*173.1±29.6*	*175.4±29.1*	*148.6±16.2*
T40	158.5±33.4	178.4±36.2	*180.7±33.7*	157.4±19.0
T100	162.5±32.1	191.6±40.0	185.6±35.3	166.4±19.7
T220	173.6±33.7	187.4±31.4	213.0±54.6	170.4±19.2
Activated partial thromboplastin time (seconds)				
BSLN	25.6±7.0	23.2±3.3	23.4±4.6	22.1±3.4
T0	23.7±5.5	22.1±4.5	22.2±2.9	*20.5±3.8*
T40	22.9±5.3	22.9±4.1	22.0±2.9	21.8±6.1
T100	23.3±5.7	22.8±4.9	21.7±2.9	*20.2±3.5*
T220	24.8±7.3	22.0±3.8	21.6±2.9	*20.5±3.5*
von Willebrand factor (%)				
BSLN	126.1±22.0	118.3±19.0	114.1±11.9	140.8±30.0
T0	125.3±19.5	114.0±14.2	113.4±12.5	138.8±32.2
T40	*148.3±22.8*	*146.9±17.9*	*126.3±11.5*	*178.3±43.4*
T100	*167.4±27.2*	*173.6±20.3*	*146.4±13.9*	*204.6±55.6*
T220	*190.6±25.9*	*195.3±34.4*	*167.4±20.8*	*214.9±52.0*
Antithrombin III (%)				
BSLN	89.6±6.0	91.0±3.6	94.3±7.4	90.1±3.3
T0	*83.3±5.0*	*84.3±3.5*	*87.1±7.3*	*80.4±3.8*
T40	*83.8±7.6*	*84.9±5.1*	*87.4±7.0*	*83.3±5.1*
T100	88.3±6.0	88.4±3.2	92.8±6.7	*85.6±3.3*
T220	89.3±7.4	92.3±3.3	94.3±6.3	87.3±4.1

Results are presented as mean±SD. Statistical significance is achieved by a value of p<0.05. Values significantly different from BSLN are denoted in italics.
BSLN, baseline; REBOA, resuscitative endovascular balloon occlusion of the aorta; TXA, tranexamic acid.

and REBOA would increase the onset of thromboembolic events and organ ischemia. Future studies may wish to look at the combined therapeutics in a coagulopathy model for further evaluation of its effectiveness. A review of clinical applications of TXA have shown its efficacy in a wide range of patients with hemorrhage from dental extractions to more severe polytrauma and cardiac surgery.[35] As this study was meant to evaluate the additive effect of TXA with REBOA in a simple hemorrhage model, further studies should look at more severe trauma models which include uncontrolled hemorrhage and blunt trauma. Another limitation is the short survival period. We are unable to extrapolate long-term survival data, but the design of the study was to specifically look at short-term development of thromboembolism and ischemic injuries. This time frame has previously demonstrated changes in coagulation function.[21] In translating the data to humans, it would be expected that any detected coagulopathy would be addressed, and longer-term survival would be dependent on the variable treatments given beyond the initial resuscitation.

CONCLUSIONS

Overall, the combination of REBOA+TXA appears safe. This model was designed to have a significant hemorrhage, but not to be fatal. As such there is no way to comment on overall survival benefit. Rather, these data support that there is not a safety concern about the additive treatment. All significant changes were expected results of REBOA deployment and not attributable to additional TXA treatment. This suggests that the combined use of REBOA and TXA, a common practice as well as a clinical practice guideline based recommendation in the military setting,[36] can capitalize on the beneficial effects of both therapies without increasing thromboembolic outcomes within the first few hours of use.

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REFERENCES

1 Eastridge BJ, Hardin M, Cantrell J, Oetjen-Gerdes L, Zubko T, Mallak C, Wade CE, Simmons J, Mace J, Mabry R, *et al*. Died of Wounds on the Battlefield: Causation and Implications for Improving Combat Casualty Care. *J Trauma Acute Care Surg* 2011;71:S4–8.
2 Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, Mallett O, Zubko T, Oetjen-Gerdes L, Rasmussen TE, *et al*. Death on the battlefield (2001-2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg* 2012;73:S431–7.
3 Kisat M, Morrison JJ, Hashmi ZG, Efron DT, Rasmussen TE, Haider AH. Epidemiology and outcomes of non-compressible torso hemorrhage. *J Surg Res* 2013;184:414–21.
4 Morrison JJ, Percival TJ, Markov NP, Villamaria C, Scott DJ, Saches KA, Spencer JR, Rasmussen TE. Aortic balloon occlusion is effective in controlling pelvic hemorrhage. *J Surg Res* 2012;177:341–7.
5 Stannard A, Morrison JJ, Scott DJ, Ivatury RA, Ross JD, Rasmussen TE. The epidemiology of noncompressible torso hemorrhage in the wars in Iraq and Afghanistan. *J Trauma Acute Care Surg* 2013;74:830–4.
6 Long B, Hafen L, Koyfman A, Gottlieb M. Resuscitative Endovascular Balloon Occlusion of the Aorta: A Review for Emergency Clinicians. *J Emerg Med* 2019;56:687–97.
7 Romagnoli A, Teeter W, Pasley J, Hu P, Hoehn M, Stein D, Scalea T, Brenner M. Time to aortic occlusion: It's all about access. *J Trauma Acute Care Surg* 2017;83:1161–4.
8 Roberts I, Shakur H, Coats T, *et al*. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess* 2013;17:1–79.
9 Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg* 2012;147:113–9.
10 Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I, Kayani A, Geer A, Ndungu B, Fawole B, *et al*. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *The Lancet* 2018;391:125–32.
11 Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. *JAMA Surg* 2013;148:218–25.
12 Schauer SG, April MD, Naylor JF, Wiese J, Ryan KL, Fisher AD, Cunningham CW, Mitchell N, Antonacci MA. Prehospital Administration of Tranexamic Acid by Ground Forces in Afghanistan: The Prehospital Trauma Registry Experience. *J Spec Oper Med* 2017;17:55–8.
13 Fisher AD, Carius BM, April MD, Naylor JF, Maddry JK, Schauer SG. An Analysis of Adherence to Tactical Combat Casualty Care Guidelines for the Administration of Tranexamic Acid. *J Emerg Med* 2019;57:646–52.
14 Myers SP, Kutcher ME, Rosengart MR, Sperry JL, Peitzman AB, Brown JB, Neal MD. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg* 2019;86:20–7.
15 Adair KE, Patrick JD, Kliber EJ, Peterson MN, Holland SR. TXA (Tranexamic Acid) Risk Evaluation in Combat Casualties (TRECC). *Trauma Surg Acute Care Open* 2020;5:e000353.
16 Committee on Trauma. *Advanced trauma life support (atls) student course manual*. 10th edn. American College of Surgeons, 2018.
17 Haider AH, Crompton JG, Oyetunji T, Stevens KA, Efron DT, Kieninger AN, Chang DC, Cornwell EE 3rd, Haut ER. Females have fewer complications and lower mortality following trauma than similarly injured males: a risk adjusted analysis of adults in the National Trauma Data Bank. *Surgery* 2009;146:308–15.
18 Jones AR, Miller J, Brown M. Epidemiology of Trauma-Related Hemorrhage and Time to Definitive Care Across North America: Making the Case for Bleeding Control Education. *Prehosp Disaster Med* 2023;38:780–3.
19 Stigall KS, Neidert LE, Morgan CG, Hemond PJ, Brown DR, Salas M, Hathaway EN, Tiller MM, Cardin S, Glaser JJ. Therapeutic cardiac arrest as an adjunct to resuscitative endovascular balloon occlusion of the aorta: Bridging the gap from fatal hemorrhage to definitive surgical control in swine. *J Trauma Acute Care Surg* 2021;90:369–75.
20 Cralley AL, Moore EE, Sauaia A, Carani PH, Schaid TR Jr, DeBot M, Fragoso M, Ghasabyan A, Hansen K, Cohen MJ, *et al*. REBOA for the Treatment of Blast Polytrauma: Zone 3 Provides Cerebral Perfusion, Attenuates Organ Dysfunction and Reperfusion Coagulopathy Compared to Zone 1 in a Swine Model. *J Trauma Acute Care Surg* 2023;94:718–24.
21 Mulier KE, Greenberg JG, Beilman GJ. Hypercoagulability in porcine hemorrhagic shock is present early after trauma and resuscitation. *J Surg Res* 2012;174:e31–5.
22 Hutin A, Levy Y, Lidouren F, Kohlhauer M, Carli P, Ghaleb B, Lamhaut L, Tissier R. Resuscitative endovascular balloon occlusion of the aorta vs epinephrine in the treatment of non-traumatic cardiac arrest in swine. *Ann Intensive Care* 2021;11:81.
23 Markov NP, Percival TJ, Morrison JJ, Ross JD, Scott DJ, Spencer JR, Rasmussen TE. Physiologic tolerance of descending thoracic aortic balloon occlusion in a swine model of hemorrhagic shock. *Surgery* 2013;153:848–56.
24 Glaser JJ, Neidert LE, Morgan CG, Brenner M, Stigall KS, Cardin S. Resuscitative endovascular balloon occlusion of the aorta for thoracic trauma: A translational swine study. *J Trauma Acute Care Surg* 2020;89:474–81.
25 Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic Acid for Trauma Patients: A Critical Review of the Literature. *J Trauma Acute Care Surg* 2011;71:S9–14.
26 Shakur H, Roberts I, Fawole B, Chaudhri R, El-Sheikh M, Akintan A, Qureshi Z, Kidanto H, Vwalika B, Abdulkadir A, *et al*. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *The Lancet* 2017;389:2105–16.
27 Herbert K, Buchbinder L, Seshachellam V, Lee L. Resuscitative Endovascular Balloon Occlusion of the Aorta and Concomitant Tranexamic Acid for Cesarean Hysterectomy Complicated by Common Femoral Artery Thrombosis: A Case Report. *Cureus* 2020;12:e11197.
28 Hajmurad OS, Choxi AA, Zahid Z, Dudaryk R. Aortoiliac Thrombosis Following Tranexamic Acid Administration During Urgent Cesarean Hysterectomy. *A & A Case Reports* 2017;9:90–3.

29 Laverty RB, Treffalls RN, McEntire SE, DuBose JJ, Morrison JJ, Scalea TM, Moore LJ, Podbielski JM, Inaba K, Piccinini A, *et al*. Life over limb: Arterial access-related limb ischemic complications in 48-hour REBOA survivors. *J Trauma Acute Care Surg* 2022;92:723–8.
30 Rivas L, Estroff J, Sparks A, Nahmias J, Allen R, Smith SR, Kutcher M, Carter K, Grigorian A, Albertson S, *et al*. The incidence of venous thromboembolic events in trauma patients after tranexamic acid administration: an EAST multicenter study. *Blood Coagul Fibrinolysis* 2021;32:37–43.
31 Russo RM, Lozano R, Ruf AC, Ho JW, Strayve D, Zakaluzny SA, Keeney-Bonthrone TP. A Systematic Review of Tranexamic Acid-Associated Venous Thromboembolic Events in Combat Casualties and Considerations for Prolonged Field Care. *Mil Med* 2023;188:e2932–40.
32 Glaser JJ, Neidert LE, Morgan CG, Brenner M, Stigall KS, Cardin S. Resuscitative endovascular balloon occlusion of the aorta for thoracic trauma in the setting of platelet dysfunction: A translational swine study. *J Trauma Acute Care Surg* 2020;89:708–15.
33 Scalea T, Glaser JJ, Burdette AJ, Gamble WB, Parsell D, Neidert L, Matsumura Y, Kozar R, Teeter W. Monitoring Organs Susceptible to Ischemia/Reperfusion Injury after Prolonged Resuscitative Endovascular Balloon Occlusion of the Aorta in a Hemorrhagic Shock Swine Model. *Panam J Trauma Crit Care Emerg Surg* 2020;9:169–80.
34 Sondeen JL, Hanson MA, Prince MD, de Guzman R, Polykratis IA, Aden JK 3rd, Cap AP, Dubick MA. Double-blinded, placebo-controlled study of early tranexamic acid treatment in swine uncontrolled hemorrhage model. *J Trauma Acute Care Surg* 2016;80:81–8.
35 Ockerman A, Vanassche T, Garip M, Vandenbriele C, Engelen MM, Martens J, Politis C, Jacobs R, Verhamme P. Tranexamic acid for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review. *Thrombosis J* 2021;19:1–6.
36 Glaser J, Stigall K, Cannon J, *et al*. Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for hemorrhagic shock (CPG ID: 38). *J T S Clin Pract Guideline* 2020:1–28.