Committee on Tactical Combat Casualty Care
Meeting Minutes
2-3 August 2011

Portland, OR

Attendance:

CoTCCC Members:

COL (RET) Frank Anders	USA
Dr. James Bagian	University of Michigan
Dr. Howard Champion	USUHS
COL Jim Czarnik	SHAPE
COL (RET) Tom Deal	VA
COL Warren Dorlac	USAF Trauma Consultant
COL Brian Eastridge	USA Trauma Consultant
COL Warner Farr	SOCCENT
COL Jonathan Jaffin	Office of the Surgeon General, USA
Dr. Donald Jenkins	Mayo Clinic
SOCM Shawn Johnson	NSWG2
CAPT Kenneth Kelly	Tripler AMC
Dr. James Kirkpatrick	AMEDD Center and School
LTC Russ Kotwal	USASOC
LTC Robert Mabry	ISR
Dr. Norman McSwain	Tulane University
MSG Harold Montgomery	75th Ranger Regiment
Dr. Edward Otten	University of Cincinnati
Mr. Gary Pesquera	Marine Corps Forces Command
Dr. Peter Rhee	University of Arizona
HSCM Glenn Royes	USCG
HMCM Eric Sine	3rd Marine Division
Mr. Richard Strayer	JSOMTC
HMC Jeremy Torrisi	Marine Corps Special Operations Command

CoTCCC and Defense Health Board Staff:

Dr. Frank Butler	CoTCCC
Ms. Danielle Davis	CoTCCC
Dr. Stephen Giebner	CoTCCC
COL Wayne Hachey	DHB
Ms. Olivera Jovanovic	DHB
Ms. Hillary Peabody	DHB

Guests:

HMCM Jared Akers	NECC
Col Jeff Bailey	C-STARS
Dr. David Baer	ISR
Mr. Keith Beaulieu	C-STARS Baltimore
CAPT Linda Beltra	BUMED
Dr. Peter Blain	Newcastle University, UK
Mr. John Bini	WHMC
Dr. Jeffery Cain	SWAT, McKinney TX
HM1 Heather Casey	HQMC HSS
CDR Martha Cutshall	HQMC HSS
CAPT Bruce Cohen	NECC
SMSgt David Dahl	ACC/SG
LtCol Sundeep Dhillon	UK Ministry of Defense
MSG John Dominguez	Civil Affairs
LT Brian Drzewiecki	FMBT-West
MSG Ian Dunbar	95th CA BDE
Mr. Duke Dunnigan	USSOCOM
Dr. Robert Foster	OSD (Retired)
Dr. Thomas Gross	FBI
Dr. Ben Hatano	OTSG Japanese Medical LNO
MAJ Keary Johnston	DMMPO
COL Andy Jose	OTSG British Liaison Medical Officer
Mr. Kevin Joyner	MARCORSYSCOM
Mr. Win Kerr	JSOMTC
MSG Chris Kosorieck	AMEDD C+S
Mr. Joshua Knapp	ATF
Ms. Kelly Hughes	USSOCOM
Mr. Jeff Luciano	USSOCOM TCCC PMO
Mr. Mark Lueder	PHTLS
Mr. Lyle Lumsden	State Dept
Dr. Perry Malcolm	OSD
Dr. Robert Mazzoli	VCoE West
LCDR Anne McKeague	NAMRU-SA
Mr. John Miles	FMTB East
SFC Daniel Morissette	75th Ranger Regiment
HMCS Sean Miles	Naval Special Warfare Group Two
Mr. Jeff Mott	CPDM (TCMC)
CPT Matthew Nichols	EMS Fellow/BAMC
COL Ricardo Ong	MAMC
CDR Nora Perez	NAMRU-SA
MAJ Brandi Ritter	DMMPO
LTC Kevin Riley	AFSOC
Dr. James Ross	NAMRU-SA
MAJ Erin Savage	Canadian Forces

Dr. Micheal Sheetz	Washington County Sherriff Office, OR
MSG Kyle Sims	USASOC
COL Colleen Shull	DMMPO
Major Greg Siebert	AF Med Support Agency
CAPT Robert Sorenson	MARFORCOM
MSG John Steinbaugh	USASOC
Ms. Misty Talley	C-Stars Baltimore
LT Darren Thomas	USMC Mountain Warfare Training Center
Mr. Scott Williams	USSOCOM TCCC PMO
SFC Fred Ziems	USASOC

Tuesday 2 August 2011
CoTCCC Public Session

Administrative Remarks **Dr. Frank Butler**

Dr. Butler called the meeting to order and asked CoTCCC members and guests to introduce themselves. All attendees were reminded to sign the attendance roster. Dr. Butler reviewed the agenda for the day and asked that individuals present at the meeting reveal any financial interests in the agenda items to be discussed. Dr. Butler noted that Mr. Chris Murphy from Combat Medical Systems was present at the meeting in order to answer any technical questions about the Combat Ready Clamp (CRoC) that might be encountered during the discussion of the proposed change to the TCCC Guidelines regarding that device. No other financial interests were declared.

Dr. Butler requested that members and guests let him know about potential candidates for future combat medic presentations.

The next meeting of the CoTCCC will be held on 15-16 November 2011 in conjunction with a meeting of the Defense Health Board (DHB) 14-15 November. These meetings will be held in the Hilton Crystal City in Arlington, VA.

The next DHB Core Board meeting will be held on August 8th at Madigan Army Medical Center. Dr. Jenkins, Chair of the Trauma and Injury Subcommittee, and MSG Harold Montgomery will brief the Core Board on the outcomes from this CoTCCC meeting.

Combat Medic Presentation **SSG Peter Contardo**

SSG Contardo is an 18D Special Forces (SF) medic attached to the 20th Special Forces Group. He presented a casualty scenario from Afghanistan in which he cared for two casualties injured by an IED. The operation took place in a village near Kandahar that was being used by the enemy as a base of operations in the area. The mission was a clearing operation to establish a landing zone in preparation for a permanent presence. The operational plan included primary TACEVAC by air to Role III, with a contingency plan to move casualties by ground to Role II. His unit consisted of 7 U.S. Special Forces and 25 Afghani personnel.

The unit successfully fought its way into the village, and established compounds for its continued operations. At about 2100, SSG Cantardo heard a blast outside his compound. He grabbed his aid bag and rushed outside into a dust cloud to treat the casualties that had been sustained in the blast. Visibility was nil and he had to follow voices to find the casualties. Locating the casualties was a significant problem and it took about a minute to find them. Two men had been injured when one of them stepped on a pressure-plate IED that had been constructed with ball bearings to provide fragmentation effect.

Casualty #1 suffered a partial amputation of his left upper extremity and amputations of both lower extremities with active hemorrhage. Casualty #2 sustained

multiple facial lacerations, had active bleeding from a large laceration at his left temple, and complained that he could not see.

Upon initial assessment, SSG Contardo found Casualty #1 alert, oriented, and speaking without difficulty. He was not able to palpate a femoral or radial pulse, however, and there was heavy bleeding from the posterior aspects of the stumps of both lower extremities. SSG Contardo applied tourniquets to all 3 injured limbs, established IV access (succeeding on the 3rd attempt), and pushed 500 mL of normal saline. For pain, he gave the casualty 10 mg of morphine sulfate IM and 10 mg IV along with OTFC and 25 mg of IV promethazine. He also gave the casualty Invanz.

Casualty #2 was alert and oriented, but complained that he could not see. He had multiple superficial facial lacerations, and a large laceration to his left temple that was actively bleeding. He was in no respiratory distress and was able to speak without difficulty. SSG Contardo applied a pressure dressing to be bleeding laceration and determined that the casualty had extensive bilateral corneal abrasions.

The casualties were treated in the field for approximately 60 minutes before the evacuation helicopter arrived. The casualty's blood pressure was approximately 80 systolic by the time he was evacuated.

SSG Contardo's comments, observations, and lessons learned from this scenario were:

1) IO access may have been a better first option than IV access for casualty #1 and allowed access to have been gained more quickly;

2) The TCCC Casualty Card must be filled out clearly in order to be useful;

3) Analgesia must be managed very carefully in patients with significant blood loss and the potential for going into hypovolemic shock;

4) IV/IO fluid challenge with crystalloids to prevent or treat shock carries the risk of contributing to a decrease in hemoglobin concentration.

In the question and answer period that followed, the following points were addressed:

- Dr. Otten asked if SSG Contardo carried Hextend as well as NS – he did.
- There was a question about which IO device was used – it was the FAST-1.
- MSG Sims asked whether hemostatic agents would have been useful – SSG Contardo replied that he had Combat Gauze, but that effective hemorrhage control was accomplished with the tourniquets.
- Dr. Rhee noted that it is difficult to start an IV working with night vision goggles.

TCCC Update **Dr. Frank Butler**

Dr. Butler noted that for 15 years, TCCC has been using the scenario of the sole Israeli casualty suffered in the raid on Entebbe to illustrate the principles of Care Under Fire. The scenario was taken from the book "Spec Ops" with the author's permission. The author, Admiral Bill McRaven, has recently been selected to command the U.S. Special Operations Command.

Heath Affairs has confirmed that permanent baseline funding (as opposed to OCO supplement funding) for the Joint Theater Trauma System (JTTS) has now been approved.

CAPT Jeff Timby, the II MEF (Forward) Surgeon, has received authorization from his command to begin fielding and using both the Combat Pill Pack and OTFC in his unit.

The manuscript entitled "Eliminating Preventable Death on the Battlefield" by LTC Russ Kotwal and his co-authors has been accepted for publication in Archives of Surgery and should be available as an e-pub within the next several weeks.

Dr. Butler noted that the CoTCCC may need to revisit the "Skill Set by Provider Level" chart with additional blood products and additional IV medications now being included in the TCCC guidelines.

Release of the final report from the Army SG's Task Force on Dismounted Complex Blast Injury casualties is still pending.

The Defense Health Board on 14 June approved the TACEVAC and Dried Plasma recommendations forwarded from the CoTCCC and the Trauma and Injury Subcommittee. The DHB memos on these two issues are pending

Several recent cases from the JTTS weekly trauma teleconferences were reviewed and lessons learned discussed.

Publications

The CoTCCC maintains a Journal Watch to identify publications relating to TCCC. Recent articles of interest include:

<u>Hemostatic Dressings in Care Under Fire – Watters et al – J Trauma 2011</u>

- Femoral artery injury: (6 mm punch biopsy)
- 30 seconds uncontrolled hemorrhage
- Fluid resuscitation with LR at 165 ml/min to maintain baseline MAP
- Three groups: Combat Gauze (CG), Celox Gauze (XG), and standard gauze (SG)
- No external pressure
- 8 animals each group
- 120 minute study period
- All animals survived
- Post-treatment blood loss: CG 194 ML; XG 110 mL; SG 120 mL (differences not significant)
- Conclusion: Advanced hemostatic dressings did not perform better than conventional gauze in an injury and application model similar to a Care Under Fire scenario.
- Note that this reinforces the need to follow manufacturer’s instructions and use direct pressure for 3 minutes after Combat Gauze is applied.
- Dr. John Holcomb’s comment in his published review of this article was: “Why does regular gauze do so well in Portland and so poorly in almost every other study around the world?”

Hemostatic Agents in Narrow Wound Tracts – Littlejohn et al – Acad Em Med 2011

- Pig model – limited access injury
- Complete transection of femoral A/V in the depth of a wound tract
- Compared Combat Gauze, Celox-A, Chitoflex, WoundStat, and Kerlix
- 16 animals per arm
- No splenectomy
- 45 seconds bleeding; 500 cc Hespan fluid resuscitation
- 5 minutes direct pressure
- Kerlix (control) mortality was 19%
- Overall mortality was 24%
- No agents superior to standard gauze (Kerlix)
- WoundStat inferior – mortality 44%
- 2 unexplained early deaths with WoundStat – pulmonary emboli?
- The study concluded that no difference was found between the hemostatic agents tested with respect to initial hemostasis, rebleeding, and survival.
- This study reinforces that bleeding models different from the standard model developed at the USAISR conference on this topic may produce different results.

Hetastarch in Trauma Patients – Lissauer et al – Am J Surg 2011

- Retrospective study of 2,225 trauma patients in Baltimore
- 497 received hetastarch (450/0.7)
- Acute kidney injury was defined as a rise in creatinine > 2x baseline
- "There were no resuscitation protocols in place during the study period. Fluid choice was based on physician preference."
- ISS different: Hetastarch 29.7; No hetastarch 27.5
- Mortality: Hetastarch 21%; No hetastarch 11%
- Acute kidney injury: Hetastarch 13%; No hetastach 8%
- Mean volume of hetastarch infused was 725 mL
- Prehospital vs ED? PRBCs/plasma as other option?
- Conclusion: "Because of the detrimental association with renal function and mortality, hetastarch should be avoided in the resuscitation of trauma patients."
- "It has been argued that a damage controlled resuscitation of a massively bleeding patient with plasma and blood may be beneficial. In this regard, abandoning synthetic colloids in favor of plasma may be appropriate."

UK Advisory Group on Military Medicine **Professor Peter Blain**

The United Kingdom Advisory Group on Military Medicine (AGOMM) chaired by Professor Blain was established in the U.K. Defense Ministry in 2008 as an extension and expansion of the Advisory Group on Medical Countermeasures (AGMC). The old AGMC had initially provided expert advice on immunizations and then followed with medical interventions for CBR. In 2008, the charter of the group was expanded as a result of the need for timely expert opinion on a wider variety of topics. The broadened

scope of the new AGOMM includes a broad range of operational medical needs, new medical interventions, and defining capability gaps in specific areas.

The AGOMM is a Non-Departmental Public Body providing independent expert medical advice (especially on urgent operational requirements) to the Secretary of State for Defense. It also works with the UK Surgeon General's office on specific issues. There is only one Surgeon General for the UK military and he is the Executive Officer on the AGOMM; each of the military services has its own Director General.

The areas of expertise of the group's members include medicine, medical ethics, and law. Considered medical advice can be rendered in 24-48 hours. The system is now undergoing a 3-year review.

The AGOMM has subcommittees on Special Medical Countermeasures and Medical Implications of Less Lethal Technologies, along with working groups in such areas as vaccination policy, blood-borne viruses, hemostatics, trauma, and battlefield analgesia. The AGOMM responds to requests from the Secretary of State's Office, the SG's Department, other Ministry of Defense departments (e.g. – CBRN Policy), service Medical Departments, and operational commands.

JTTS Deployed Director: Pre-Hospital Care Comments **COL Jeff Bailey**

Col Bailey is an Air Force trauma surgeon who recently returned from a tour as the Deployed Director of the JTTS. His team was in theater from fall 2010 to spring 2011. Col Bailey focused his talk on three primary issues:

1. Registry of Point-of-Injury and Transfer Data - An article on this topic was published recently in the Journal of Trauma which reports that the U.S. military medical system documented pre-hospital care for less than 25% of casualties early in OEF and OIF. JTTS personnel working on TACEVAC issues developed better approaches to documentation and improved collection to 70% in a trial period.

2. Aeromedical Platforms - It is not possible at present to statistically compare the outcomes from treatment provided in the different TACEVAC models being used in theater. The platforms are used differently and are therefore difficult to evaluate in this way. Outcomes in TACEVAC may reflect decisions made by the Patient Evacuation Coordination Center (PECC) as well as care rendered.

3. Surgical Airways - In the field and in TACEVAC platforms, finding the tracheal lumen is hard, even with good conditions. There are several cases in the JTTR where inserted airway control devices completely missed the lumen. COL Bailey suggested the CoTCCC examine the "Emergent Surgical Airway, Easy as 1,2,3" training program which includes use of an elastic bougie.

SOCMSSC TCCC Issues **Mr. Win Kerr**

Mr. Kerr presented an overview of the Special Operations Combat Medical Skills Sustainment Course (SOCMSSC). SOF medics are required by USSOCOM directive to attend this knowledge and skills refresher course at a minimum of every two years as long as they are acting as medics. Course topics include BLS, ACLS, PEPP, TCCC,

trauma skills, extraction techniques, non-trauma topics, and after-action/lessons learned reviews. The course is 9 days long; there are 22 courses per year and 42 seats per course.

Each day of SOCMSSC begins with a student working through a trauma scenario using moulaged manikin casualties. This is followed by a thorough review in which the student is critiqued by his instructors and his peers. This technique has been well-accepted by faculty and students as a highly effective training technique. The course culminates in a Field Training Exercise that covers all three phases of TCCC.

TCCC guidelines provide the foundation for trauma management in the SOCMSSC. Students are expected to know and apply the TCCC Guidelines using sound tactical medical judgment. The following areas are emphasized:

- Care Under Fire
  - Paintball "enemy fire"
  - Casualty contact minimized
  - CAT-T/SOFT-T
- Tactical Field Care
  - Vertical incision for cricothyroidotomy
  - Hemostatic dressings
  - Halo chest seal - primary dressing for chest trauma
  - Primary and alternate needle decompression sites for tension pneumothorax
  - Hextend
  - Hypothermia Prevention and Management Kit
- Tactical Evacuation Care
  - TCCC Casualty card
  - Fluid warming devices
  - Electronic monitoring devices

Mr. Kerr touched on a list of topics for which the faculty is seeking clarification or further guidance. The list includes such topics as hyperventilation in the management of severe TBI patients, elevating the head of the litter to 30 degrees in severe TBI patients, ketamine/midazolam for analgesia, optimal resuscitation techniques for hypovolemic shock, hypertonic saline, and the validity of the radial pulse as an indicator of adequate perfusion. The CoTCCC is viewed as their primary source of guidance for these questions.

Feedback to the Field **MAJ Brandi Ritter**

MAJ Ritter presented the latest edition of Feedback to the Field, a collaborative effort of DMMPO and AFME to highlight areas where process improvement might be of benefit. A previous edition reported several complications from surgical airways. In the more recent series, thirteen cases in which surgical airways had been performed were identified. A variety of tubes were used with internal diameters varying from 6 to 10 mm. Vertical incisions were used in 8 of the procedures. The tubes were found to be outside the trachea in three cases. This edition of Feedback will soon be posted on the Defense Technical Information Center website.

Another counterfeit tourniquet has been identified in Combat Lifesaver kits purchased to support the Afghanistan National Army and Afghanistan National Police. These kits were found in U.S. Troop Medical Clinics at Baghram Air Base. The quality is inferior and it does not stop arterial flow when tested against established criteria. Approximately 56,000 were ordered, but the source has not yet been identified.

Discoloration of supposedly sterile H+H gauze packs was noted in IFAKS in December 2010 and contamination is suspected. Results of microbial testing are pending. If fungal contamination is found, the question of possible contribution to an observed increase in fungal wound infections in wounded warriors will arise. Guidance is forthcoming on this topic.

A number of cases of failed extraction of sternal IO needles have been seen in Kandahar. The original version of the PYNG FAST-1 IO device with removal tools expired in 2010 and should no longer be in use, but they are still showing up. The current model is not supposed to require a removal tool, but removal has been noted to be a problem on occasion.

On a positive note, it was announced that the Air Force has made the decision to add chest seals and eye shields to their IFAKs. The Marine Corps is adding 4 eye shields to each of their Combat Lifesaver sets.

PHTLS TCCC Courses **Mr. Mark Lueder**

Six new TCCC teaching sites have been added by PHTLS , including Virginia Tech, for a total of 18 sites in the U.S. 122 TCCC courses have been taught to date, graduating 923 providers. Programs are also being rolled out in eight Latin American countries, with more in the works. TCCC will be among the course offerings at the EMS Expo in Las Vegas later this month. Mr. Lueder called for volunteer instructors. The instructor cadre is growing, but the need is still significant.

TCCC Equipment Evaluation **Dr. Frank Butler**

Dr. Butler presented an update on the TCCC Equipment Evaluation project, which is now up and running. The project is being executed by the Naval Operational Medical Lessons Learned Center (NOMLLC) and is being conducted entirely online. It solicits input from combat Medics, Corpsmen, and PJs who have treated combat casualties on the battlefield at any time during the Global War On Terror. While the information obtained will not be attributed to individuals in the compiled reports, identification of the submitting individual is required. Evaluations are not accepted if there is no name or valid e-mail address included or if multiple evaluations are submitted from the same e-mail address.

Medical equipment recommended in the TCCC Guidelines is evaluated for effectiveness on a scale of 1 to 5, with 1 representing the lowest (worst) score and 5 representing the highest (best) score. To date, 54 evaluation forms have been submitted, providing feedback based on the treatment of 1853 reported casualties. Dr. Butler presented early data from this project. A summary of the evaluations received to

date will be added to the TCCC website materials the next time the sites are updated. An overview of this project will be published soon in the NOMLLC newsletter.

Proposed Change: Junctional Tourniquet **MSG Harold Montgomery**

The junctional areas are the groin, the buttocks, the axilla, the shoulder girdle, and the base of the neck. There is an urgent need for improved methods of hemorrhage control in these areas, especially the groin. Preliminary data from an ongoing review of recent fatalities at Dover being conducted by COL Eastridge and LTC Mabry indicates that junctional hemorrhage has overtaken non-compressible hemorrhage as the most common cause of preventable battlefield deaths. This increase is associated with the increased incidence of dismounted IED attacks in southern Afghanistan, which has an injury pattern that typically includes proximal lower extremity amputations and junctional hemorrhage in the groin. A formal requirements document addressing this need for better methods of hemorrhage control in this region already exists. As with any intervention recommended for use by combat medics, efficacy is paramount. Ease of training and a small weight and cube are also very important.

The Combat Ready Clamp™ (or CRoC™) from Combat Medical Systems is one such device designed to control junctional hemorrhage.

The CRoC weighs 1.5 pounds; its stored dimensions are 3.5” high x 11.5” wide x 1.5” deep; and it costs $445.00 per unit. It is FDA approved (510k) as a device to apply direct pressure over packed inguinal wounds and to occlude the external iliac artery when applied at a point midway between the anterior superior iliac spine and the pubic tubercle. The device has been tested in a groin application on perfused cadavers and

publication of the results is pending. Further testing, to include application by combat medics on live volunteers with blood flow assessed by doppler ultrasound and pulse palpation, is planned. Evaluation of the CRoC for use in other locations is also planned.

MSG Montgomery reviewed the manufacturer's instructions for proper application. The CRoC cannot be applied in traditional live tissue training models. It does clamp down well on human subjects and is resistant to dislocation during movement. Further information on the effect of using the device on a casualty whose pelvis has been fractured would be of benefit.

The Army Special Missions Unit and the 75th Ranger Regiment currently field the CRoC and it is now being used by Houston Life Flight. There is one known clinical use of the CRoC in the treatment of a wounded enemy combatant. Unpublished reports indicate that it was successful in controlling the junctional hemorrhage, but that the casualty died of other wounds.

MSG Montgomery recommends adding the CRoC to the TCCC Guidelines at the end of paragraph (4.b.) of the Tactical Field Care guidelines, and paragraph (3.b.) of the Tactical Evacuation Care guidelines, the sections that deal with hemorrhage control. Dr. McSwain noted that the CRoC has the potential to create a crush injury to the bowel if used above than the inguinal ligament. Dr. Champion also noted that the device must have a firm surface on the on the anatomy against which to be tightened, such as the muscles between the pubic tubercle and the anterior superior iliac spine. This requires application at or below the level of the inguinal ligament. Discussion of this recommended change will be continued in tomorrow's internal session.

Proposed Change: Needle Decompression **Dr. Butler for Mr. Don Parsons**

Mr. Don Parsons, the sponsor for this proposed change, was unable to attend the meeting due to a last-minute schedule change. Dr. Butler presented Mr. Parsons' material.

A specific casualty scenario presented in a recent JTTS weekly teleconference sparked discussion on this topic. In this mounted IED attack, a soldier sustained closed head trauma resulting in loss of consciousness. The soldier lost his vital signs in the prehospital setting. CPR was being performed when he arrived at the hospital. Bilateral needle chest decompression performed in the Emergency Department resulted in a rush of air from a left-sided tension pneumothorax. This was followed by a return of vital signs.

This case illustrates the value of making a presumptive diagnosis of tension pneumothorax in a casualty with known torso trauma or polytrauma when the casualty suffers a cardiac arrest. When the casualty is in such extremis, the possibility of causing a decrement in his or her clinical status by performing bilateral needle decompressions is nil. For a casualty in this clinical situation, there is a great deal to gain and nothing to lose by using needle chest decompression to rule out tension pneumothorax.

The proposed change to the TCCC Guidelines also recommended using needles as large as 10 gauge for needle chest decompression in addition to the currently used 14 ga, 3.25 inch needles. There are anecdotal reports in the Joint Theater Trauma Registry and weekly trauma teleconferences of multiple needle chest decompressions

being required for casualties suspected of having a tension pneumothorax. The 14 gauge catheters may be kinking or clotting and a larger catheter may be more resistant to these developments.

Discussion of this recommended change will be continued in tomorrow's internal session.

Proposed Change: Tranexamic Acid (TXA) **Col Warren Dorlac**

Hemorrhage continues to be the leading cause of preventable death among combat casualties. Patients at the greatest risk of exsanguination often present with a clinically significant coagulopathy. The activation of fibrinolysis accompanying the massive generation of thrombin in the period immediately following trauma has been well described and can occasionally overwhelm clot formation. Such hyperfibrinolysis occurs in the most severely injured patients and is an omen of a poor outcome.

TXA is an anti-fibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot breakdown rather than promoting new clot formation. The safety and efficacy of using TXA to treat trauma patients was recently evaluated in a large (over 20,000 patients) trial called "The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage" (CRASH-2). In that study, TXA use resulted in a statistically significant reduction in all-cause mortality, with the greatest reduction in mortality seen in the sub-group of most severely injured patients. Further subgroup analysis suggested that the survival benefit of TXA was greatest in those patients given TXA within one hour of injury; this benefit was less but still present in patients given TXA between one and three hours after injury. Patients given TXA more than three hours after injury had a decreased survival compared to controls. There was no difference in the rate of vascular occlusive events between the two arms of the study and no major incidence of other medication-related adverse events was seen. Though CRASH-2 had some noteworthy design limitations, it provided strong evidence that TXA safely reduces mortality in bleeding trauma patients when initiated within three hours after injury.

A survival benefit from TXA use was also found in combat trauma patients. The MATTERS (Military Application of Tranexamic Acid in Emergency and Resuscitative Surgery) study is a recent review of almost 900 casualties treated at the Bastion Role III facility in Afghanistan. The MATTERS study found a significant increase in survival in those casualties who were given TXA. This effect was more pronounced in casualties who required massive transfusions; there was a 50% increase in survival in casualties who required massive transfusion.

TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg. It must be stored within a temperature range of 15-30 °Celsius / 59-86° Fahrenheit. Due to poorly defined potential interactions between Hextend® and TXA, which may blunt the antifibrinolytic activity of TXA, TXA should not be given through the same IV line as Hextend® and Hextend® should not be used as a carrier fluid for this medication.

Discussion of this recommended change will be continued in tomorrow's internal session.

Wednesday 03 August
CoTCCC Internal Administrative Session

Administrative Remarks **Dr. Frank Butler**

The Chairman called the meeting to order, had attendees sign in, and reviewed the day's agenda. No financial conflicts of interest were declared.

The next meeting of the CoTCCC will be held on 15 & 16 November at the Hilton Crystal City Hotel in Arlington, VA. The next meeting of the DHB core board will be on 14 November. In conjunction with the November COTCCC meeting, there will be a Tenth Anniversary CoTCCC dinner to recognize the group's ten years of working together to improve the care provided to U.S. and coalition partner casualties.

Automated Fire Extinguishing Systems and Inhalation Injury **Dr. Steve Giebner**

In the combat casualty scenario presented by MSG Dean Bissey at the February 2011 meeting, casualties were treated in a still-smoking vehicle after the Automated Fire Extinguishing System (AFES) had discharged to suppress a fire in the crew compartment. Later in the scenario, both the casualties and providers experienced shortness of breath while in the TACEVAC helicopter. These pulmonary symptoms were attributed to exposure to the fire suppression agent Halon.

The commercial term "Halon" refers to a family of chemicals (halogenated alkanes) that have a variety of industrial uses. Several of them were used in fire extinguishing systems in the past. The one most commonly employed in military ground vehicles was Halon 1301. This compound could rapidly extinguish fires inside crew compartments without reaching levels harmful to humans. Halon 1301 and the other Halons were phased out of use by the military in the late 1990s because of their deleterious effect on atmospheric ozone.

Halon 1301 was replaced in military ground vehicles by a new halogenated alkane, HFC-227ea, which has virtually no effect on atmospheric ozone. When combined in an AFES with sodium bicarbonate, the system can extinguish crew compartment fires in less than 250 ms while generating minuscule and harmless amounts of fluorine, hydrogen fluoride, and other byproducts.

In this combat casualty scenario, it is impossible to determine after the fact precisely what specific agent caused the pulmonary symptoms in the casualties and healthcare providers. Since smoke was still being produced inside the vehicle, the casualties may have suffered smoke inhalation or been exposed to a variety of toxins produced by the burning of materials in the vehicle. When an AFES discharges as designed, neither the fire suppression agents nor their byproducts of combustion should reach levels inside the passenger compartment sufficient to produce pulmonary damage. The imperative to remove both casualties and first responders from burning vehicles remains strong, however, because of the risk of harm from fire, ammunition "cooked off" by heat, smoke, and toxic products of combustion from the fire.

Combat Medic Presentation Review **Group**

The Committee returned to a discussion of the combat medic presentation from yesterday. Several points were noted:

- How can we better train medics to treat casualties in a near-zero visibility environment? Note that NVGs do not help in a scenario such as this.

- The medic used normal saline to resuscitate a casualty even though he had Hextend with him. There are other uses for normal saline (wound irrigation, treatment of dehydration) and medics commonly carry it with them. Since all of the combat medical schoolhouses are teaching Hextend for fluid resuscitation in casualties with hypovolemic shock, the continuing use of NS or LR probably arises from the need to train unit medical officers in TCCC, as has been noted previously.

- The medic gave morphine sulfate IM. Faster analgesia could have been obtained with fentanyl lozenges or IV morphine. The comment about unit-based training above applies to this item as well. The comment was also made that as long as morphine auto-injectors are still issued to medics, they will continue to be used.

- Eye shields were not used on casualty #2. Injuries suspected to be corneal abrasions at first look may in fact be penetrating eye injuries. These injuries are best treated with eye shields and oral or IV antibiotics in the field.

- Elevation of the head 30 degrees above the horizontal (done by raising the litter, not by flexing the neck) and other proposed new interventions for the first responder management of TBI will be reviewed by Dr. Otten and presented at the next meeting.

Proposed Change: Needle Decompression **Group**

After further discussion of this proposed change, the CoTCCC voted to approve the recommended change to the TCCC Guidelines as shown in Appendix 1. The group noted that there has been no documentation of improved efficacy from using a larger needle and that increased potential for iatrogenic injury from the procedure was a concern with the larger gauge needles. This change was approved by vote of 39 for and 1 against with 2 abstentions.

Proposed Change: Junctional Tourniquet **Group**

Central to this discussion is the recent increase in dismounted IED attacks that typically result in complex blast injuries; this injury pattern includes traumatic amputation of at least one and often both lower extremities. The amputations are often quite high, making tourniquet placement difficult. The leg injuries are often accompanied by urogenital injuries, penetrating pelvic and abdominal trauma, and upper extremity injuries. Although Combat Gauze has been anecdotally reported to work well in some cases, a backup means of hemorrhage control is needed for cases where tourniquets and Combat Gauze are not effective. The recent CoTCCC RDT&E priorities list calls for

new technologies to control junctional bleeding. The Combat Ready Clamp™ (CRoC) is such a technology.

After further discussion of this proposed change, the CoTCCC voted to approve the recommended change to the TCCC Guidelines as shown in Appendix 2. This change was approved by vote of 38 for and 2 against with 2 abstentions.

Proposed Change: Tranexamic Acid (TXA) **Group**

TXA has now been shown to significantly increase survival in two major studies, one in civilian trauma patients and one in military casualties. The evidence for this agent is presented in Appendix 3. The CoTCCC voted to approve the proposed change with the wording as noted in the Appendix by a vote of 38 for and 2 against with 2 abstentions.

The following points will be addressed in the TCCC curriculum and in the explanatory text for the next edition of the PHTLS Manual:

- TXA (or intravenous trade name: Cyklokapron)
- The treating medic must be trained in TXA use and administration.
- TXA must be maintained at a temperature between15-30 °Celsius / 59-86° Fahrenheit.
- Once reconstituted, it should be administered within 24 hours.
- TXA should be first administered as soon as possible after injury but should NOT be initiated more than 3 hours after wounding.
- It should NOT be administered through the same line being used for blood products (to include PRBCs, thawed plasma, and rFactor VIIa) or Hextend.
- TXA is given in 100 ml of NS or LR over 10 minutes intravenously or intraosseously. Do not administer as an IV push (may cause hypotension).
- After administration of the first dose, mark on chest wall (and TCCC card) “1 gm TXA given”
- Administer Hextend or blood products as indicated
- Administer second dose of TXA if still in the field after fluids are in
- After administration of the second dose, change chest wall (and TCCC card) marking to “2 x 1gm TXA given”

FK Butler

_____ 14 October 2011

Frank K. Butler, M.D. Date
CAPT, MC, USN (Ret)
Chairman

FKB:sdg

Appendix 1

Proposed Change – Needle Decompression

8 August 2011

Mr. Don Parsons

Current Wording (TCCC Guidelines 101101)

Tactical Field Care

17. Cardiopulmonary resuscitation (CPR)
    Resuscitation on the battlefield for victims of blast or penetrating trauma who have no pulse, no ventilations, and no other signs of life will not be successful and should not be attempted.

Tactical Evacuation Care

N/A

Proposed Change

Tactical Field Care

17. Cardiopulmonary resuscitation (CPR)
    Resuscitation on the battlefield for victims of blast or penetrating trauma who have no pulse, no ventilations, and no other signs of life will not be successful and should not be attempted. **However, casualties with torso trauma or polytrauma who have no pulse or respirations during TFC should have bilateral needle decompression performed to ensure they do not have a tension pneumothorax prior to discontinuation of care. The procedure is the same as described in section 3 above.**

Tactical Evacuation Care

16. Cardiac Arrest during TACEVAC

a. Casualties with torso trauma or polytrauma who have no pulse or respirations during TACEVAC should have bilateral needle decompression performed to ensure they do not have a tension pneumothorax. The procedure is the same as described in section 2 above.

b. CPR may be attempted during this phase of care if the casualty does not have obviously fatal wounds and will be arriving at a facility with a surgical capability within a short period of time. CPR should not be done at the expense of compromising the mission or denying lifesaving care to other casualties.

Discussion

Needle chest decompression (NDC) in traumatic cardiac arrest may be lifesaving if an unsuspected tension pneumothorax is present. Empiric bilateral NDC should be performed for any casualty with known or suspected chest trauma or polytrauma who suffers cardiorespiratory arrest. In a recent case presented in the Joint Theater Trauma System weekly trauma teleconference, this intervention was responsible for saving the life of a casualty in traumatic cardiac arrest. This procedure is routinely performed by many or most emergency physicians before discontinuing care for a trauma patient who has suffered a cardiac arrest.

References

1. Army Surgeon General Letter 25 Aug 2006, (Management of Soldiers with a Tension Pneumothorax) Discusses use of a 14 gauge 3.25 inch needle catheter.
2. Thoracostomy in a Swine Model of Traumatic Tension Hemopneumothorax, Prehospital Holcomb, John B., McManus, John G., Kerr, S. T. and Pusateri, Anthony E. Emergency Care,13:1,18 — 27
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5. Blunt head trauma or extensive tension pneumothorax? Buschmann C, Hunsaker J, Correns A, Tsokos M: Forensic Sci Med Pathol 2011;Epub ahead of print
6. CoTCCC Meeting minutes – April 2011

Appendix 2

Proposed TCCC Guidelines Change

8 AUG 2011

MSG Harold Montgomery

Issue

Combat Ready Clamp

Current Wording in the TCCC Guidelines

Care Under Fire

7. Stop *life-threatening* external hemorrhage if tactically feasible:
   - Direct casualty to control hemorrhage by self-aid if able.
   - Use a CoTCCC-recommended tourniquet for hemorrhage that is anatomically amenable to tourniquet application.
   - Apply the tourniquet proximal to the bleeding site, over the uniform, tighten, and move the casualty to cover.

Tactical Field Care

4. Bleeding
   a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2-3 inches above wound.
   b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than two hours), use Combat Gauze as the hemostatic agent of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no traumatic brain injury (TBI).
   c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2-3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.
   d. When time and the tactical situation permit, a distal pulse check should be

accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side by side and proximal to the first, to eliminate the distal pulse.

e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

TACEVAC Care

3. Bleeding

a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2-3 inches above wound.

b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than two hours), use Combat Gauze as the hemostatic agent of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no TBI.)

c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2-3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.

d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side by side and proximal to the first, to eliminate the distal pulse.

e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Proposed Change

*** Proposed changes in red text**

Care Under Fire

7. Stop *life-threatening* external hemorrhage if tactically feasible:

- Direct casualty to control hemorrhage by self-aid if able.
- Use a CoTCCC-recommended tourniquet for hemorrhage that is anatomically amenable to tourniquet application.
- Apply the tourniquet proximal to the bleeding site, over the uniform, tighten, and move the casualty to cover.

Tactical Field Care

4. Bleeding

a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2-3 inches above wound.

b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than two hours), use Combat Gauze as the hemostatic agent of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no traumatic brain injury (TBI). **If a lower extremity wound is not amenable to tourniquet application and cannot be controlled by hemostatics/dressings, consider immediate application of mechanical direct pressure including CoTCCC recommended devices such as the Combat Ready Clamp (CRoC).**

c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2-3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.

d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side by side and proximal to the first, to eliminate the distal pulse.

e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

TACEVAC Care

3. Bleeding

a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2-3 inches above wound.

b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than two hours), use Combat Gauze as the hemostatic agent of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for

hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no TBI.) **If a lower extremity wound is not amenable to tourniquet application and cannot be controlled by hemostatics/dressings, consider immediate application of mechanical direct pressure including CoTCCC recommended devices such as the Combat Ready Clamp (CRoC).**

c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2-3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.
d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side by side and proximal to the first, to eliminate the distal pulse.
e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Discussion

There has been a recent increase in dismounted blast injury (most commonly an IED attack) with traumatic amputation of one or both lower extremities. The leg injuries are often accompanied by urogenital injuries, penetrating pelvic and abdominal trauma, and upper extremity near or complete amputation. The amputations are often quite high.

DCBI casualties are often noted to have life-threatening bleeding in the groin or very proximal lower extremity regions, where a tourniquet cannot be successfully applied. Although Combat Gauze has been reported anecdotally to be working well, a backup means of hemorrhage control is need for cases where Combat Gauze is not effective. (Kinzle 2011, CoTCCC Meeting Minutes – November 2010)

Both the recent OTSG Dismounted Complex Blast Injury Task Force and the recent CoTCCC RDT&E priority list call for new technologies to control junctional bleeding. The CRoC is such a technology.

USAISR has evaluated a junctional tourniquet, the Combat Ready Clamp (CRoC) and found it to be a promising technology for controlling hemorrhage in junctional regions such as the groin and axilla. Further development and evaluation of this technology is planned. At least two SOF units have deployed this device into theater.

References

Kinzle R: Development of a Field Packable Junctional Tourniquet. ISR MilTech report; 21 Jan 2011

Kragh JF, Murphy C, Dubick MA, Baer DG, Johnson J, Blackbourne LH: New Tourniquet Device Concepts for Battlefield Hemorrhage Control. AMEDD Journal; Apr-Jun 2011

Procedure: Combat Ready Clamp Application. Ranger Medic Handbook, 4th edition; Hammesfahr, Montgomery, Chou

Appendix 3

Tranexamic Acid (TXA) in Tactical Combat Casualty Care Guideline Revision Recommendation Committee on Tactical Combat Casualty Care 11 August 2011

Purpose: To provide a comprehensive review of the use of tranexamic acid (TXA), examine specified and implied actions, apply classification of recommendations and level of supporting evidence, and submit a recommendation for the revision of the guidelines in Tactical Field Care and Tactical Evacuation Care.

Background/Discussion:

Medicine is a science of uncertainty and an art of probability. Sir William Osler
The Tactical Combat Casualty Care (TCCC) guidelines, first characterized for special operations forces by Butler in 1996, identify three stages of care: (1) care under fire; (2) tactical field care; and (3) tactical evacuation care. The guidelines have been revised through a series of regularly scheduled meetings of the Committee on Tactical Combat Casualty Care (CoTCCC), a panel comprised of civilian and military medical personnel with experience in trauma and combat operations. A 2/3 majority vote of full membership of the COTCCC is required to approve a change to the TCCC guidelines. Although the guideline revision process is a rigorous academic endeavor, systematic classification of recommendations and level of supporting evidence has only recently been performed. The current guidelines, however, do not address new developments learned in the study of antifibrinolytics for the adjunct management of hemorrhage in trauma.

The changes approved by the Committee below address these new advances. Additionally, for more than 20 years, the American College of Cardiology (ACC) and the American Heart Association (AHA) have released clinical practice guidelines to provide recommendations on care of patients with cardiovascular disease. The ACC/AHA guidelines currently use a grading schema based on level of evidence and class of recommendation. The levels of evidence include:

- Level of evidence A: recommendation based on evidence from multiple randomized trials or meta-analyses;
- Level of evidence B: recommendation based on evidence from a single randomized trial or nonrandomized studies;
- Level of evidence C: recommendation based on expert opinion, case studies, or standards of care.

The classes of recommendation include:

- Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective;

- Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
- Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy;
- Class IIb: usefulness/efficacy is less well established by evidence/opinion;
- Class III: conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Of 2711 specific recommendations, only 11% of recommendations are supported by level of evidence A, whereas 48% are level of evidence C. Only 19% of class I recommendations have level of evidence A. [1]

In addition to prior Level B and C literature supporting TXA use based on Phase I and Phase II clinical trials, there is now Level A evidence supporting the addition of tranexamic acid to the guidelines for the treatment of hemorrhage in civilian and now specifically combat casualties. The CRASH-2[2] study was performed prospectively with civilian trauma patients and the MATTERS[3] study was performed retrospectively but specifically in combat casualties using the latest advanced treatment and resuscitation protocols at the single busiest center in CENTCOM. While a randomized prospective clinical trial in US combat casualties would be ideal, this is not permitted under DoD restrictions.

With these limitations in supporting evidence, the TCCC guidelines have always been dependent on the preponderance of evidence from animal studies, civilian and military trauma experience and expert opinion from military medical personnel ranging from trauma and orthopedic surgeons, emergency and critical care physicians, as well as corpsmen and medics with experience in managing combat casualties.

This paper utilizes the ACC/AHA grading schema for level of evidence and class of recommendation to support the guideline revision recommendation for Tranexamic Acid administration in Tactical Field Care and Tactical Evacuation Care incorporating recent literature and expert opinion.

Current Recommendations for Tranexamic Acid administration in TCCC:

Care under fire: None

Tactical Field Care: None

Tactical Evacuation Care: None

Recommended TCCC Revisions:

Care under fire: None

Tactical Field Care and Tactical Evacuation Care:
(Create #6 Adjunct Medications) BEFORE IV Fluids

- If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)
  - Administer 1 gram of tranexamic acid in 100 cc in NS or LR as soon as possible but NOT later than 3 hours after injury.
  - Begin second infusion of 1 gm TXA after Hextend or other fluid treatment.
  - Move Fluid Resuscitation to a NEW #7

Add to Text:

- (TXA or intravenous trade name: Cyklokapron) in 100 ml of 0.9% NS or LR over 10 minutes intravenously or via interosseous device.
- Once reconstituted, it should be administered within 24 hours.
- It should NOT be administered through the same line being used for blood products (to include rFactor VIIa) or Hextend. Do not administer as an IV push (may cause hypotension).
- After administration of the first dose, mark on chest wall "1 gm TXA given"
- After administration of the second dose, change chest wall marking to "2 x 1gm TXA given"

CAVEATS
Drug should be first administered as early as possible but NOT initiated beyond 3 hours from wounding.
Treating medic must be trained in drug use and administration.
Drug must be properly maintained between15-30 °Celsius / 59-86° Fahrenheit.

Classes of Recommendation and Level of Evidence

I. Early administration of 1 gram of TXA to casualties who are anticipated to receive blood transfusions

a. Recommendation: Class I

b. Specified/Implied Actions:

- Hemorrhage is a common contributor to death in combat casualties (Level B)
- Hemostatic resuscitation improves survival (Level B)
- Antifibrinolytics (specifically TXA) have been shown to decrease bleeding in hemophilia and menorrhagia (Level B)

- Tranexamic acid has FDA approval to decrease bleeding in hemophilia and menorrhagia (Level B)
- Tranexamic acid has been shown to benefit civilian trauma patients (Level B)
- Tranexamic acid has been shown to benefit combat casualties when a rigorous hemostatic resuscitation is followed (Level B)
- Early administration (<3 hours) of TXA after injury appears to improve survival (Level B)
- Arrival to Level II and III care facilities in a combat setting within three hours of injury are not guaranteed (Level C)
- Storage of TXA in field conditions will be problematic with its temperature limitations (Level C)
- Identification of who needs TXA, administration of TXA and monitoring for complications requires skills of an advanced practice medic (Level C)

- Level of Evidence: B

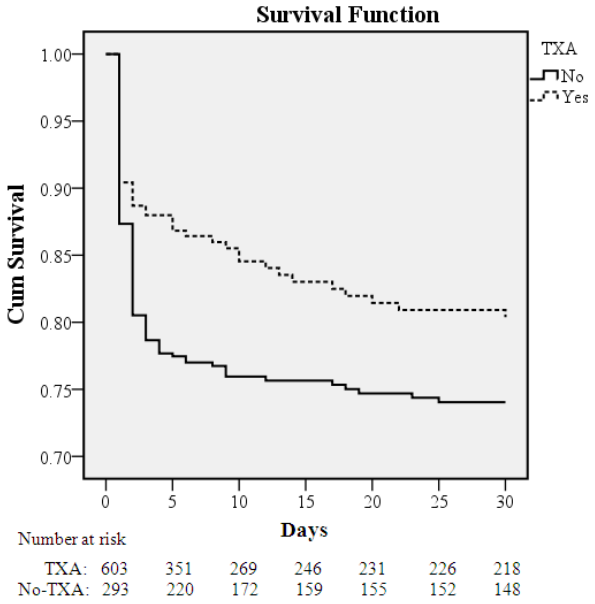
SUPPORTING INFORMATION FOR THE USE OF TRANEXAMIC ACID (TXA) in TCCC

1. **Background.**
   a. Hemorrhage is the leading cause of preventable death among combat casualties. Patients who require a massive blood transfusion (greater than 10 PRBCs within 24 hours) have an improved survival when an early aggressive hemostatic resuscitation is followed. Patients at the greatest risk of exsanguination often present with a clinically significant coagulopathy that has recently been linked to systemic anticoagulation through a Protein C-dependent pathway, and activation of fibrinolysis.[4] The activation of fibrinolysis accompanying the massive generation of thrombin in the period immediately following trauma has been well described and is readily observed by the elevated levels of D-dimers, fibrin split products (FSP) and plasmin-antiplasmin complexes found in blood samples drawn from trauma patients on presentation.[5] Fibrinolysis can occasionally overwhelm clot formation following trauma, a phenomenon that can be directly observed in real time by thromboelastography (TEG) or rotational thromboelastometry (ROTEM). Such hyperfibrinolysis occurs only in the most severely injured patients (approximately 4% of trauma patients in major civilian US trauma centers) and portends extremely poor outcomes.[6, 7]
   b. Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in a surgical patients. The safety and

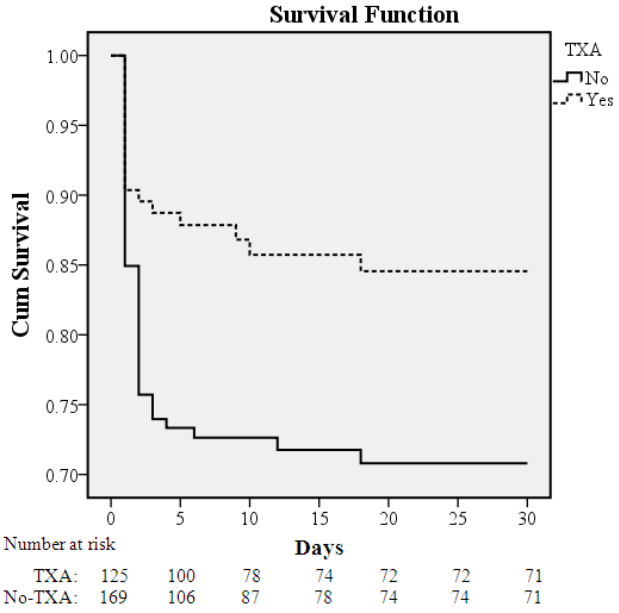
efficacy of using TXA to treat trauma patients was recently evaluated in a large randomized, placebo-controlled clinical trial called "The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage" (CRASH-2) [1]. In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with, or at risk of, significant bleeding (HR>110, SBP<90, clinical judgment) were randomized to either TXA or placebo administered as a loading dose of 1gram over 10 minutes followed by an infusion of 1 gram over 8 hours. The primary outcome was death in hospital within 4 weeks of injury. Secondary outcomes included vascular occlusive events, transfusions, and surgical interventions. Patients were randomized and treated within 8 hours of injury. Patients were excluded from randomization only if the treating physician considered the patient to have either a clear indication for use of TXA or a clear contraindication. This randomization scheme reflects application of the uncertainty principle, or clinical equipoise in decision-making. Only 14 patients out of 20,225 screened were excluded from randomization, because they died before they could be randomized. [8] The treatment and placebo groups were well-balanced across a wide range of prognostic variables. The overall mortality rate in the cohort studied was 15.3%, of whom 35.3% died on the day of randomization. A total of 1063 died due to hemorrhage; 59.9% of these died on the day of randomization. A subgroup at particularly high risk of death included those patients presenting with a SBP<75 (3,161 of 20,125; 15.7%). Overall, this study included a large and very diverse trauma population, with most patients facing a relatively low mortality risk. Nevertheless, over 3,000 patients in the study would likely have been candidates for treatment under a damage control resuscitation (and possibly massive transfusion) procedure. The authors reported that TXA use resulted in a statistically significant reduction in the relative risk of all-cause mortality of 9% (14.5% vs. 16.0%, RR 0.91, CI 0.85-0.97; p = 0.0035). This 1.5% absolute risk reduction means that one would have to treat 67 trauma patients with TXA to prevent one from dying of any cause (number needed to treat = 1/absolute risk reduction). Note that this NNT reflects the underlying mortality risk in the CRASH-2 study (15%). The authors also reported a reduction in relative risk of death due to bleeding of 15% (4.9% vs. 5.7%, RR 0.85, CI 0.76-0.96; p = 0.0077). Similarly, the authors reported a relative risk reduction in death due to bleeding on the day of randomization of 20% (2.8% vs. 3.5%, RR 0.80, CI 0.68-0.93; p = 0.0036). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. Further subgroup analysis suggested that the benefit of TXA was greater in patients treated within 3 hours of injury compared to those treated later and in patients with a presenting systolic blood pressure of ≤ 75 mmHg compared to those with normal systolic blood pressures. There was no difference in rate of vascular occlusive events between the two arms of the study

(1.7% for TXA vs. 2.0% for placebo, p = 0.084). No unexpected adverse events were reported. There were no differences in need for transfusion or surgery between the two arms (blood product transfused in 50.4% of patients for TXA vs. 51.3% for placebo, p = 0.21; any surgery in 47.9% of patients for TXA and 48.0% for placebo, p = 0.79). A recent post-hoc analysis of the CRASH-2 data suggests that the greatest benefit of TXA administration is likely to occur when patients receive the medication soon after injury. In this analysis, TXA given between 1 and 3 hours post-trauma reduced the risk of death due to bleeding by 21% (147/3037 [4.8%] vs. 184/2996 [6.1%], RR 0.79, CI 0.64-0.97; p=0.03). Treatment given after 3 hours seemed to increase the risk of death due to bleeding (144/3272 [4.4%] vs. 103/3362 [3.1%], RR 1.44, CI 1.12-1.84; p=0.004).[9]

c. **TXA experience in combat-related hemorrhage**: A recent registry-based study of combat injured troops receiving blood in Afghanistan (January 2009 - December 2010) at the Bastion Role 3 facility has demonstrated findings supportive of TXA use in this population. In a review of 896 combat casualties treated at Bastion over this time frame, 32.7% (N=293) received TXA (mean ± SD dose: 2.3 ± 1.3g) while 67.2% (N=603) did not receive TXA. In the overall cohort, the TXA group was more severely injured (ISS: 25.2±16.6 vs. 22.5±18.5; p<0.001), required more blood (11.8±12.1 vs. 9.8±13.1 pRBC units; p<0.001), and had a lower Glasgow Coma Score (7.3±5.5 vs. 10.5±5.5; p<0.001) and initial systolic blood pressure (112±29.1 vs. 122.5±30.3 mmHg), but also had a lower unadjusted mortality than the no-TXA group (17.4% vs. 23.9%; p=0.028). In the massive transfusion cohort (N=321; 24 hour transfusion: 21.9±14.7 pRBC; 19.1±13.3 FFP and 3.5±3.2 apheresis platelet units), mortality was also lower in the TXA (mean ± SD dose: 2.4 ± 1.4g) compared to the no-TXA group (14.4% vs. 28.1%; p=0.004). In a multivariate regression model, TXA use in the massive transfusion cohort was independently associated with survival (odds ratio: 7.28; 95% confidence interval: 3.02-17.32. For all patients requiring at least one unit of blood after combat injury, patients receiving TXA had higher rates of DVT (2.4% vs. 0.2%, p = 0.001) and PE (2.7% vs. 0.3%, p =0.001), but were also more likely to have injury patterns associated with higher risk of thromboembolic events ; including higher mean ISS (25 vs 23, p < 0.001), more severe extremity injuries (extremity AIS >=3 66.6% in TXA group, 47.3% non-TXA, p < 0.001), and more commonly GCS < or = 8 (63.3% vs. 35.6%, p < 0.001). These survival benefit findings associated with TXA use support the hypothesis that the use of this adjunct, in conjunction with component-based resuscitation following combat injury, is associated with improved survival. This association is most prominent in those requiring massive transfusion. [2]



Kaplan-Meier survival curve of the overall cohort, patients receiving TXA or no-TXA, p = 0.006 (Wilcoxon Statistic)



Kaplan-Meier survival curve of the massive transfusion group receiving TXA^{MT} or no-TXA^{MT}, p = 0.004 (Wilcoxon Statistic).

2. **TXA Mechanism**
   a. TXA is an anti-fibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot break-down rather than promoting new clot formation. TXA (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a small

molecule (MW 157.2) inhibitor of plasminogen activation, and inhibitor of plasmin activity. It occupies the lysine-binding sites on plasminogen thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circulating plasmin prevents binding to fibrin, and thus prevents clot break-down.

b. TXA is 10 times more potent *in vitro* than an older drug of the same class, aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. Dosing should be adjusted for renal impairment, but no adjustment is needed for hepatic impairment. TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

3. FDA position

a. FDA-approved use: Intravenous administration of TXA (under the brand name Cyklokapron®, Pfizer) was approved by the FDA in 1986 for short-term use (2-8 days) for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures.

The FDA approved use of the oral form of TXA (Lysteda™, Ferring Pharmaceuticals) for menorrhagia (to control heavy menstrual cyclic bleeding) in 2009.

b. Unlabeled use: **Although tranexamic acid is an FDA-approved drug and has undergone a gamut of regulatory and clinical testing, it is not specifically an FDA-approved indication to stop uncontrolled hemorrhage in severe trauma patients.** The antifibrinolytic effect of tranexamic acid was first reported in 1966.[10] Tranexamic acid has been studied in many clinical settings, including hemophilia[11], intraoperative and postoperative bleeding [12] ,gastrointestinal hemorrhage [13] , traumatic hyphema[14] and hereditary angioedema [15].

c. It has been studied in randomized trials to control bleeding during surgery, and most recently in trauma as discussed above. It is widely used in non-trauma surgeries and has been used on a limited basis by at least one major US civilian trauma center (Massachusetts General Hospital).[16] It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

4. Potential adverse events with TXA:

a. Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting and diarrhea, generally dose-related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally

observed in the setting of active intravascular clotting such as thrombotic DIC). Its use is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used carefully in the setting of urinary tract bleeding as ureteral obstruction due to clotting has been reported. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates as this may increase the risk of thrombosis. Another adverse risk noted in a retrospective review in patients who had undergone pulmonary endarterectomy with hypothermia was an increase in seizure activity (when compared to aprotinin) in patients without structural brain lesions (7 versus 0, p=0.02) [17] The doses given were high dose (on the order of 3-6 times the dose used in the two trauma studies)*

5. **Considerations for Use.**
   a. TXA has been studied in patients with subarachnoid hemorrhage (SAH). TXA was shown to reduce bleeding in SAH, but increase cerebral ischemia, possibly due to vasospasm or increased microvascular thrombosis. Since TXA use had no effect on mortality or quality of life in these studies, its use is not recommended in this population. At this time, there is no role for TXA or other antifibrinolytics in managing SAH. It should be noted that treatment with TXA in these studies was modeled on the prolonged (3-4 times per day for 2-8 days) dosing used in hemophilia. A dosing regimen shorter in duration might avoid this outcome, and remains a topic for further investigation.
   b. It is worth noting, as discussed above, that the relative contraindication to using antifibrinolytics in SAH was known prior to the initiation of CRASH-2. Thus, it is possible that treating physicians tended to exclude patients with TBI from trial enrollment. Nevertheless, about 18% of patients had a GCS score of 3-8 (17.8% for TXA, 18.2% for placebo), probably indicating severe TBI, and 13.4% had GCS scores of 9-12 (p>0.05, NS, for both groups), indicating moderate TBI. Mild or no TBI (GCS 13-15) was present in 68.7% (TXA) and 68.3% (placebo). While GCS scores can be depressed for a variety of reasons such as global hypoperfusion, it would be reasonable to expect that a substantial fraction of trauma patients with depressed GCS had in fact sustained a TBI. The authors did report that death from head injury was the same in both groups (6.0% for TXA and 6.2% for placebo, RR 0.97, CI 0.87-1.08, p=0.6). They also reported that stroke rates (0.6% for TXA and 0.7% for placebo) and neurosurgery rates (10.3% for TXA and 10.5% for placebo) were similar between the groups. These data are reassuring; if a major safety concern were present for perhaps one third of the patients in the trial (those with depressed GCS among whom TBI patients are common) a negative effect on outcomes would be expected.

c. Critics of the CRASH-2 study have noted that it would have been helpful to know outcomes for patients' with TBI, since TXA has not proven to be beneficial in subarachnoid hemorrhage (SAH). As a result, the CRASH-2 Intracranial Bleeding Study was a prospective randomized controlled trial nested within the CRASH-2 trial, conducted to quantify the effects of an early short course (1 g over 10 minutes, within 8 hours of injury) of TXA on intracranial hemorrhage in patients with TBI. [18] This portion of the trial involved 270 patients who had a documented head injury (GCS $\leq$14 and an abnormal CT scan of the head) and were at risk of significant extracranial bleeding (133 patients allocated to TXA and 137 allocated to placebo), and found new focal cerebral ischemic lesions occurred in 6 (5%) patients in the TXA group, compared to 12 (9%) in the placebo group (RR 0.51, CI 0.18-1.44). Mortality was higher in the placebo group (18% for placebo, 11% for TXA, RR 0.47, CI 0.21-1.04). In addition, mean total hemorrhage growth was higher in the placebo group. This trial shows that neither moderate benefits nor moderate harmful effects can be excluded, however, the analyses suggest that TXA might improve outcomes for patients with TBI and should be further evaluated in future research. The CRASH-3 trial will further examine the effectiveness of the early administration of a short course of TXA in patients with TBI.
d. Hextend® is commonly used as a resuscitation fluid in trauma patients. Several studies have demonstrated that this product may interfere with hemostasis through a number of mechanisms including fibrinolysis. Due to poorly defined potential interactions between Hextend® and TXA, which may blunt the antifibrinolytic activity of TXA, TXA should not be given through the same IV as Hextend®, and Hextend® should not be used as a carrier fluid for this medication.
e. Use of TXA in conjunction with pro-coagulant drugs sometimes administered to trauma patients, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex concentrate (APCC), could result in thrombotic complications. Of note, only 17 patients enrolled in the CRASH-2 trial received Novoseven (13 in the TXA group and 4 in the placebo group). It is also possible that a subgroup of patients not identified in the CRASH-2 trial, such as those with traumatic brain injury, may be at particularly high risk of thrombotic or other complications if treated with TXA. It is very reassuring, however, that no increase in vascular occlusive events was observed in this study, despite the significantly increased baseline risk of such complications in this population. The rate of deep vein thrombosis reported is difficult to interpret due to the lack of a consistent screening procedure, and the variable clinical importance of this complication. However, the rates of myocardial infarction, stroke and pulmonary embolism may be more informative. These complications are relatively simple to diagnose, and are of clinical importance. None of these complications were more common in

the treatment arm, while myocardial infarction was significantly less common in the TXA group (p=0.035). These data strongly argue against a safety problem with respect to vascular occlusive events.

6. **Considerations for Use.** TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.
   a. Infuse 1 gram of tranexamic acid in 100 ml of 0.9% NS over 10 minutes intravenously (more rapid injection has been reported to cause hypotension). Hextend® should be avoided as a carrier fluid.
   b. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9% NS carrier***.***
   c. ***There are presently no data from randomized controlled trials to support administration of further doses to trauma patients.***

7. **Storage**
   a. Room temperature (15-30 °Celsius / 59-86° Fahrenheit)

8. **Guidelines for administration in the deployed setting.**
   a. The early use of TXA should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion (e.g., significant injury and 3 or 4 risk factors/indicators of massive transfusion).
   b. Use of tranexamic within 3 hours of injury is associated with the greatest likelihood of clinical benefit. **The greatest benefit was seen when TXA was administered within 1 hour of wounding.** Due to this time constraint, the uncertainty of battlefield evacuation and a good safety profile in the doses previously used in trauma patients, use in the prehospital setting is recommended if patient monitoring and storage requirements can be met. For these reasons, use by advanced practice medics only is recommended. (Advanced practice medics are defined as: SOF 18D or Paramedic to include PJ, SOAR, FP-C)

9. **Benefits:** In an evaluation on TXA use by the military, Maj Andrew Cap made the following analysis:

   a. Approximately 25% of the roughly 6,000 soldiers who died between the OIF and OEF conflicts to date had potentially survivable injuries (1,500 soldiers). Theoretically, if all 1,500 had been treated with TXA, and the group had experienced a reduction in mortality of 1.5% as in the CRASH-2 trial, 23 lives would have been saved at a cost of about $5,200 per life ($120,000 overall). For perspective, the cost to the US military of procuring one unit of packed red blood cells is approximately $100 (personal communication, COL F.

Rentas, Director, Armed Services Blood Program Office, July 2010). This does not include the costs of blood storage and shipment to theater, disposables and nursing time associated with blood administration, or blood unit cross-matching. The costs of administering TXA are thus substantially lower than the costs of administering one unit of red blood cells.

b. In a paper supplied in response to an RFI to USAISR about preventable deaths due to non-compressible hemorrhage, the following estimate was provided by the CoTCCC:

Non-Compressible Hemorrhage
How Many Lives Could Have Been Saved in Iraq or Afghanistan If We Had Had an Effective Intervention?
22 August 2010

Note: The exact answer to this question unknowable. The methodology below is one way to postulate a reasonable approximation to this question.
If you take the Kelly paper (J Trauma 2008) and use that as a starting point:

- Total fatalities in both groups: 982
- Total potentially preventable deaths: 232
- % of fatalities that were potentially preventable (both groups): 24%
- Potentially preventable deaths from non-compressible hemorrhage: 115 (page S-23)
- % of total fatalities that were both potentially preventable and resulted from non-compressible hemorrhage: 12%

Then taking the number of fatalities in OEF and OIF: (Washington Post fatality numbers as of 22 Aug 10)

- OEF 1220
- OIF 4403
- Total 5623

Using the 12% of total fatalities that were both potentially preventable and that resulted from non-compressible hemorrhage as calculated above and applying that to the total fatalities in OEF/OIF:

- 675 estimated potentially preventable fatalities due to non-compressible hemorrhage

The hardest part of the equation is determining what fraction of these estimated 675 potentially preventable fatalities (due to non-compressible hemorrhage) might have been saved by tranexamic acid. Based on the most relevant data in wartime injuries (from the MATTERS paper) the potential benefit, or the number of patients required to treat with TXA to achieve a mortality benefit of one patient, was 7. This translates to a potential 96 US lives saved had TXA been used.

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