

Surgical adjuncts to noncompressible torso hemorrhage as tools for patient blood management

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Despite the tremendous advances and successes in the care of combat casualties over the past 15 years of war, noncompressible torso hemorrhage (NCTH) remains the most likely source of potentially preventable death (approx. 25%) on the battlefield. This is also likely true for civilian victims of blunt and penetrating trauma. Various devices and therapeutic interventions have been, and are being, developed in an attempt to reduce morbidity and mortality for patients with NCTH. Examples include the use of prehospital blood and blood products, tranexamic acid, specially designed tourniquets for junctional hemorrhage control, retrograde endovascular balloon occlusion of the aorta, intracavity foam, expandable hemostatic sponges, and intravascular nanoparticles to suspended animation. Although each of these modalities offer the potential to staunch uncontrolled hemorrhage until an injured patient is able to reach definitive surgical care, further research and advances must be made to further reduce trauma morbidity and mortality and to identify those technologies and modalities that are best suited to rapid movement to the front lines of combat casualty care as well as to emergency medical personnel dealing with civilian trauma victims. The surgical adjuncts for NCTH discussed may all be considered as potential tools for patient blood management programs. If effective they offer the possibility of reduce hemorrhage and blood product exposure and improved patient outcomes.

SURGICAL ADJUNCTS TO NCTH

Tremendous advances have been made in combat casualty care over the past 15 years of the wars in Iraq and Afghanistan. Blood transfusion ratios, the use of whole blood, vascular shunts, tourniquet usage, the use of tranexamic acid and rapid evacuation to definitive surgical care are but a few of the advances achieved.¹ Many of these have been adopted into the civilian sector with similar levels of success. Recent data from the Joint Trauma Theater Registry indicate that combat casualties that reach a surgeon alive have a greater than 98% survival rate. While impressive, Eastridge and coworkers,² in a comprehensive review of the Department of Defense's Office of the Armed Forces Medical Examiner records of almost 5000 combat deaths, concluded that nearly 25% of personnel killed in action were potentially preventable deaths. Of the potentially preventable deaths 67% were related to truncal hemorrhage and almost 20% were related to junctional hemorrhage. In 2014, the United States Food and Drug Administration (FDA) hosted a public workshop entitled: "Hemostatic Medical Devices (HMD) for Trauma Use."³

ABBREVIATIONS: AAJT = abdominal aortic and junctional tourniquet; NCTH = noncompressible torso hemorrhage; REBOA = retrograde endovascular balloon occlusion of the aorta; RT = resuscitative thoracotomy.

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The purpose of the workshop was to obtain information on the current challenges and opportunities related to HMD for use in emergency situations. The emphasis for this workshop was the unmet need of NCTH and how the FDA was dealing with this important issue. Workshop participants discussed factors that contribute to HMD performance, reliability, and the types of studies that could potentially be used to evaluate appropriate laboratory and animal testing, bleeding control, and human factors as well as clinical data collection for these technologies. This article will review many of the nonsurgical adjuncts designed to ameliorate NCTH that were discussed at the meeting. Some are currently in use and others are in various phases of development.

The surgical adjuncts for NCTH discussed may all be considered potential tools for patient blood management programs. If effective they will reduce hemorrhage and blood product exposure, which may both improve outcomes.

Junctional tourniquets

One of the more perplexing issues facing both combat and civilian surgeons alike are wounds in the torso's junctional regions.⁴ By convention these are described as the inguinal and axillary regions. Unlike exsanguinating wounds from the extremities that are amenable to simple tourniquet placement these wounds do not lend themselves to easy compressibility and often result in fatal exsanguination despite on-scene attempts to staunch blood loss. Lyon and colleagues⁵ described the use of the abdominal aortic and junctional tourniquet (AAJT) for hemorrhage control in the junctional areas. Initially developed to compress the distal aorta, the AAJT (Fig. 1) has been used to control proximal bleeding with varying degrees of success. Taylor and colleagues⁶ report anecdotal evidence for the effectiveness of this device in a limited case series. Unfortunately, since junctional bleeding is essentially within the domain of military casualties, it is highly unlikely that definitive studies will ever be carried out to support the use of the AAJT or accurately determine its clinical effectiveness and utility in a well-controlled study. Finally, Walker and coworkers⁷ assessed tourniquet effectiveness for proximal junctional control in a retrospective autopsy review study of combat casualty deaths from the United Kingdom. Although pelvic vascular injuries above the level of the inguinal ligament made up less than 1% of the combat deaths during the study period results indicated that the vast majority of AAJT devices would be ineffective in preventing loss of life for these types of wounds.

Retrograde endovascular balloon occlusion of the aorta

Balloon occlusion of the aorta was first used in the early 1950s in the Korean War.⁸ More recently, others⁹⁻¹¹ have



Fig. 1. AAJT.

utilized various techniques and balloons to tamponade abdominal and pelvic bleeding. Retrograde endovascular balloon occlusion of the aorta (REBOA) offers an opportunity to occlude or tamponade bleeding in the abdominal and pelvic regions without having to surgically enter these cavities before adequate resuscitation of the patient. In this procedure direct surgical or percutaneous access to the femoral artery is obtained, followed by placement of a catheter with a balloon attached (either with or without fluoroscopic guidance), which allows for control of ongoing hemorrhage from the supraceliac or pelvic regions of the torso. Ideally suited for Zones I and III (central aortic and pelvic regions) hemorrhage control, it offers the advantage of not having to perform a resuscitative thoracotomy (RT) on a moribund patient with all of its subsequent morbidity and mortality. Moore and coworkers¹² recently reviewed the recent experience of two major US Level I trauma centers comparing REBOA with RT in critically injured perimoribund patients and demonstrated that REBOA offered a higher probability of survival compared to RT. This will need to be further assessed in larger patient series as the procedure becomes more widely accepted. In addition, the technology is evolving from a cut down insertion catheter to a smaller percutaneous catheter insertion. This, as well, needs further exploration and critical evaluation.

Intracavitary foam

Polyurethane foam

Recently, interest has developed in the use of self-expanding polyurethane foams to control intracavitary hemorrhage. Peev and coworkers¹³ described improved survival in a dose-dependent fashion in a swine model of intra-abdominal hemorrhage. Higher amounts of foam resulted in increased survival but also resulted in the need

for concomitant bowel resections, most likely due to the development of increased intra-abdominal pressure and the possibility of the development of abdominal hypertension.

The difficulty associated with the use of foam products is the need to obtain access to the abdominal cavity without creating additional injury. Rago and coworkers¹⁴ and Mesar and coworkers¹⁵ from Massachusetts General Hospital evaluated various methods with which to deliver the foam in a porcine model. Clinical trials of polyurethane foam delivery in humans are forthcoming. Boichichio and colleagues¹⁶ have also reported on “Gro-Klot” (currently under development and non-FDA approved) which is also polyurethane based self-expanding foam that self-pressurizes. Porcine models that were examined demonstrated significant promise in a Grade 5 liver injury model. Although polyurethane foams appear promising, the major drawback is that once removed, the hemorrhage typically resumes immediately.

Fibrin-based hemostatic foam

“ClotFoam” (currently under development and non-FDA approved) is a second-generation fibrin sealant embedded in a biomimetic complex polymer. Cross-linked in situ, ClotFoam stops bleeding from severe intracavitary trauma and achieves hemostasis without compression and/or sutures outside the operating room. It is produced in a viscous liquid phase, composed of three parts. When delivered through a CO₂ propellant, the solutions form a foamy gel that spreads throughout the peritoneal cavity to promote adhesion and stimulate the coagulation cascade. The foam enhances the distribution of active clotting agents and provides a scaffold upon which the fibrin network can be distributed and thereby adhere to and bind to lacerated tissue. ClotFoam allows noninvasive application and dissemination of the agent in the peritoneal or other body cavities, adheres and compress lacerated or wound tissue to prevent flow of blood, and maintains the necessary components over the wound to produce a platelet (PLT) plug followed by a fibrin clot that stimulates the native coagulation cascade. Rapid formation of a strong hydrogel, effective cleavage, and rapid polymerization to produce a functional fibrin clot over lacerated bleeding tissue ensures that the sealant remains at the site of application without being washed away by blood. High tensile and adhesive strength characterize the clot produced by this agent. ClotFoam’s fibrin components can be kept in solution for several weeks, ready to use. Boichichio and colleagues have reported on the efficacy of ClotFoam in several porcine studies (2015 Military Health System Research Symposium). Recently this technology received an investigational new drug approval from the FDA and Phase I human clinical trials have started at Washington University/Barnes Jewish Hospital in St Louis,

Missouri. The key advantage of this foam technology is that it does not need to be removed and is truly a hemostatic agent. This seems particularly advantageous compared to polyurethane technologies which all require surgical removal at some point after application.

Nonabsorbable, expandable, hemostatic sponge (for temporary internal use)

XStat is a first-in-kind FDA-approved hemostatic device for the treatment of gunshot and shrapnel wounds. XStat works by injecting a group of small, rapidly expanding sponges into a wound cavity using a syringe-like applicator. Each sponge contains an x-ray detectable marker. In the wound, the XStat sponges expand and swell to fill the wound cavity within 20 seconds of contact with blood. This creates a temporary barrier to blood flow and provides hemostatic pressure. XStat is considered a temporary device for use up to 4 hours until surgical care is reached. It should only be used for patients at high risk for immediate life-threatening bleeding from hemodynamically significant (Advanced Trauma Life Support Class 3 or 4 hemorrhagic shock), NCTH, and when definitive surgical care cannot be reached within minutes. XStat use is restricted to certain anatomic locations—primarily exsanguinating penetrating wounds to the extremities and cannot be used in the thorax and the pleural cavity, the mediastinum, the abdomen and retroperitoneal space, the sacral space above the inguinal ligament, or tissues above the clavicle.

Intravascular nanoparticles and synthetic PLTs

Various groups^{17,18} have developed and tested hemostatic nanoparticles that, when injected intravenously, have resulted in decreased bleeding and improved survival in rodent models of hemorrhagic shock. These particles can significantly reduce bleeding times while maintaining maximal clot firmness as demonstrated by rotational thromboelastometry. While promising, these particles are fraught with significant manufacturing difficulties. Larger animal studies and human clinical trials are well into the future. Finally, there is early investigational work on the development of synthetic PLTs based on nanotechnology.¹⁹ Initial studies have demonstrated that these synthetic PLTs reduce bleeding time by 50% in a murine model of hemorrhagic shock and are superior to other treatments for uncontrolled hemorrhage—most notably recombinant Factor VIIa.

Suspended animation

In 2000 Safar and colleagues²⁰ described a potential role for the use of suspended animation in lethal traumatic injuries that would allow time for surgical correction while protecting cerebral function. Casas and colleagues²¹ have developed a portable cardiopulmonary bypass/extracorporeal

membrane oxygenation circuit for induction of profound hypothermia in a swine model of lethal hemorrhagic injuries. Nozari and colleagues²² at the University of Pittsburgh have developed and tested, in a canine model of lethal injuries, the role for suspended animation, which allowed for the return of normal neurologic function in the vast majority of surviving animals. Despite some evidence of laboratory success, developing the right protocol and identifying appropriate candidates will be extremely difficult. Furthermore, transferring this technology to the frontline of a battlefield or the site of a civilian road traffic accident or shooting will be even more challenging. Tisherman²³ provides a concise review of suspended animation and the potential opportunities and pitfalls as this exciting field moves forward.

CONCLUSIONS

Junctional and NCTH control remains a vexing problem. Better understanding of the coagulopathy associated with traumatic injury and advances in biomechanical engineering technology are needed to solve these issues. Moreover, we will need to simplify protocols and delivery mechanisms so that frontline medics and emergency medical personnel will be able to rapidly identify potential candidates upon which to use many of the tools and techniques described above. Moreover, many of the surgical adjuncts for NCTH described are potential tools for patient blood management programs. If any are found to be effective they would be an important aspect of any program to reduce blood loss and blood product exposure.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

- Jenkins DH, Rappold JF, Badloe JF, et al. Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: definitions, current practice, and knowledge gaps. *Shock* 2014;41 Suppl 1:3-12.
- Eastridge BJ, Hardin M, Cantrell J, et al. Died of wounds on the battlefield: causation and implications for improving combat casualty care. *J Trauma* 2011;71:S4-8.
- Junctional tourniquets for controlling hemorrhage from wounds in adults: a review of clinical effectiveness, cost-effectiveness, safety, and guidelines. Canadian Agency for Drugs and Technologies in Health: Ottawa (ON); 2014.
- Lyon M, Shiver SA, Greenfield EM, et al. Use of a novel abdominal aortic tourniquet to reduce or eliminate flow in the common femoral artery in human subjects. *J Trauma Acute Care Surg* 2012;73:S103-5.
- Lyon M, Johnson D, Gordon R. Use of a novel abdominal aortic and junctional tourniquet to reduce or eliminate flow in the brachial and popliteal arteries in human subjects. *Prehosp Emerg Care* 2015;19:405-8.
- Taylor DM, Coleman M, Parker PJ. The evaluation of an abdominal aortic tourniquet for the control of pelvic and lower limb hemorrhage. *Mil Med* 2013;178:1196-201.
- Walker NM, Eardley W, Clasper JC. UK combat-related pelvic junctional vascular injuries 2008-2011: implications for future intervention. *Injury* 2014;45:1585-9.
- Stannard A, Eliason JL, Rasmussen TE. Resuscitative endovascular balloon occlusion of the aorta (REBOA) as an adjunct for hemorrhagic shock. *J Trauma* 2011;71:1869-72.
- Morrison JJ, Rasmussen TE. Noncompressible torso hemorrhage: a review with contemporary definitions and management strategies. *Surg Clin North Am* 2012;92:843-58, vii.
- Rasmussen TE, Dubose JJ, Asensio JA, et al. Tourniquets, vascular shunts, and endovascular technologies: esoteric or essential? A report from the 2011 AAST Military Liaison Panel. *J Trauma Acute Care Surg* 2012;73:282-5.
- Kragh JF Jr, Murphy C, Dubick MA, et al. New tourniquet device concepts for battlefield hemorrhage control. *US Army Med Dep J* 2011;38-48.
- Moore LJ, Brenner M, Kozar RA, et al. Implementation of resuscitative endovascular balloon occlusion of the aorta as an alternative to resuscitative thoracotomy for noncompressible truncal hemorrhage. *J Trauma Acute Care Surg* 2015;79:523-30; discussion 530-2.
- Peev MP, Rago A, Hwabejire JO, et al. Self-expanding foam for prehospital treatment of severe intra-abdominal hemorrhage: dose finding study. *J Trauma Acute Care Surg* 2014;76:619-23; discussion 623-4.
- Rago AP, Larentzakis A, Marini J, et al. Efficacy of a prehospital self-expanding polyurethane foam for noncompressible hemorrhage under extreme operational conditions. *J Trauma Acute Care Surg* 2015;78:324-9.
- Mesar T, Martin D, Lawless R, et al. Human dose confirmation for self-expanding intra-abdominal foam: a translational, adaptive, multicenter trial in recently deceased human subjects. *J Trauma Acute Care Surg* 2015;79:39-46; discussion 46-7.
- Bochicchio GV, Gupta N, Porte RJ, et al. The FINISH-3 trial: a phase 3, international, randomized, single-blind, controlled trial of topical fibrocaps in intraoperative surgical hemostasis. *J Am Coll Surg* 2015;220:70-81.
- Shoffstall AJ, Atkins KT, Groynom RE, et al. Intravenous hemostatic nanoparticles increase survival following blunt trauma injury. *Biomacromolecules* 2012;13:3850-7.
- Shoffstall AJ, Everhart LM, Varley ME, et al. Tuning ligand density on intravenous hemostatic nanoparticles dramatically increases survival following blunt trauma. *Biomacromolecules* 2013;14:2790-7.
- Bertram JP, Williams CA, Robinson R, et al. Intravenous hemostat: nanotechnology to halt bleeding. *Sci Transl Med* 2009;1:11ra22-
- Safar P, Tisherman SA, Behringer W, et al. Suspended animation for delayed resuscitation from prolonged cardiac arrest

- that is unresuscitable by standard cardiopulmonary-cerebral resuscitation. *Crit Care Med* 2000;28:N214-8.
21. Casas F, Alam H, Reeves A, et al. A portable cardiopulmonary bypass/extracorporeal membrane oxygenation system for the induction and reversal of profound hypothermia: feasibility study in a Swine model of lethal injuries. *Artif Organs* 2005;29:557-63.
 22. Nozari A, Safar P, Wu X, et al. Suspended animation can allow survival without brain damage after traumatic exsanguination cardiac arrest of 60 minutes in dogs. *J Trauma* 2004;57:1266-75.
 23. Tisherman SA. Suspended animation for resuscitation from exsanguinating hemorrhage. *Crit Care Med* 2004;32:S46-50. ■