Management of Exsanguinating Hemorrhage: What’s New?

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Disclosure

- Chair of ACS COT EMS Committee
- Authored Evidence Based Prehospital Guideline for External Hemorrhage Control
- Consultant for clinical trial design: Arsenal Inc, Sotera Wireless, Inc

What’s the Problem?

- Hemorrhage is the leading cause of early death after injury
- Leading cause of preventable death on the battlefield
- Most patients die within 6 hours of injury
Types of Hemorrhage

- External
  - Extremity
  - Junctional
  - Torso
- Internal
  - Chest
  - Abdomen
  - Retroperitoneum
    (Pelvis/Kidney)

External Bleeding: Approach

Prehospital External Hemorrhage Control Protocol

- Apply direct pressure/pressure dressing to injury

  - Direct pressure effective
    (hemorrhage controlled)

  - Direct pressure ineffective or impractical
    (hemorrhage not controlled)

  - Wound amenable to tourniquet placement
    (e.g., extremity injury)

  - Apply a tourniquet

  - Wound not amenable to tourniquet placement
    (e.g., junctional injury)

  - Apply a topical hemostatic agent
    with direct pressure

Prehospital Emergency Care 2014:18:163-173

Boston Marathon Bombing

- Widespread use of improvised tourniquets
  by bystanders
- Most ineffective, some worsened bleeding by
  only occluding venous return
- Recent publication from Boston suggested
  improvised tourniquets did not impact survival
Principles of Tourniquet Use
• Used when direct pressure is ineffective OR not practical
• Use commercially available product: windlass, pneumatic or ratcheting
  • MUST OCCLUDE ARTERIAL FLOW
• Leave tourniquet in place until definitive care* (may be exceptions for very prolonged transport)
• Note TIME of placement

Hartford Consensus Conference
• Encouraged earlier access of EMS to scenes of mass shooting
• Encouraged bleeding control training including tourniquets for all EMS, Law enforcement and bystanders

THREAT
• Threat mitigation
• Hemorrhage control
• Rapid Extrication to safety
• Assessment by Medical Providers
• Transport to Definitive care
ABC vs CAB

- CAB
  - Military
  - Tactical Civilian Emergency Care
  - Multisystem trauma with obvious arterial hemorrhage

- ABC
  - Most routine civilian trauma
  - Medical Patients

Public Training for Hemorrhage Control

B Con Course

http://www.naemt.org/education/B-Con/b-con-course-materials
Course Objectives

- Explain the rationale for early use of a tourniquet for life-threatening extremity bleeding.
- Demonstrate the appropriate application of a tourniquet to the arm and leg.
- Describe the progressive strategy for controlling hemorrhage.
- Describe appropriate airway control techniques and devices.
- Demonstrate the correct application of a topical hemostatic dressing (combat gauze).

Extremity Bleeding Case

What’s the Data?

- 20 publications of Prehospital tourniquet use for Extremity Hemorrhage
- Primarily military, One civilian (11 cases)
- Meta-analysis: survival rate 92% adults, 91% children
- Amputation rate 19%
- No amputations solely a result of the tourniquet use

Prehospital Emergency Care 2014:18:163-173
Hemostatic Agents

- 7 human studies: 5 military, 1 civilian, 1 military and civilian
- Products tested: HemCon, Celox, Quickclot granules, Quickclot gauze
- Poor quality studies but generally high rates of bleeding control (range 70% to 100%)
- Animal data suggests agents configured to facilitate wound packing perform better

Wound packing

- Need to incorporate wound packing into EMT training
- Need to have a person dedicated to maintaining wound pressure
- Gauze format preferred

IT Clamp

- New to the market
- Only 2 clinical cases reported
- Effective in swine model with small injury to femoral artery
- Human perfused cadaver model: reduced fluid loss from a variety of wounds
IT clamp

Junctional Hemorrhage

- Major vascular injury in the groin or axilla
- Too high for tourniquet placement

Junctional Hemorrhage Devices

- Abdominal Aortic Junctional Tourniquet
- Junctional Emergency treatment tool
- SAM Junctional Tourniquet
- Combat Ready Clamp
  - Groin Application
  - Umbilical application
- No data from clinical use except for case reports
Abdominal Aortic Junctional Tourniquet

- Designed for bilateral groin wounds
- Compression of abdominal aorta
- If effective would block all blood flow to both LE
- Extremely painful in normal volunteers

AAJT applied to axilla

Junctional Emergency Treatment Tool (JETT)

No clinical data
SAM Junctional Tourniquet

Combat Ready Clamp

What’s the Data

- Application to Normal volunteers: Combat ready clamp best tolerated, Abdominal Aortic Junctional Tourniquet too painful to tolerate
- Medic study: SAM and CRC easiest to apply with fastest application time, users preferred these two
- Swine and Cadaver studies
  - CRC: 2 hrs application, groin OK, abdomen: severe muscle necrosis and long term disability
  - Insufficient data to make any definitive recommendations
Summary: External hemorrhage

- Direct pressure
  - Hemostatic agents
  - Wound packing
- Tourniquets
  - When direct pressure not effective or not practical
- Junctional devices??
- IT clamp??
Internal hemorrhage

- Fluid Resuscitation
- Prehospital Blood/Plasma
- Tranexamic Acid
- Pelvic sheeting
- REBOA
- Investigational Intra-abdominal foams
- Suspended Animation

How to we identify Compensated Shock?

- Uncompensated shock
  - You know it when you see it!
  - Hypotension
  - Severe tachycardia
  - Pale, Cold, Clammy...
- Compensated Shock
  - Common in young people
  - May be subtle....

Acidosis

- Marker of the Severity of Shock
  - Arterial base deficit
  - Arterial or venous lactate
  - pH < 7.2 interferes with coagulation factors and cardiac function
  - Point of Care testing: venous lactate
Prehospital Lactate vs SBP

End Tidal Co2?
- Marker of both ventilation and perfusion
- Low ET CO2 in trauma patients may be an early sign of poor perfusion and thus compensated shock

Non-invasive pH monitoring
- Mobile CareGuide 4100
- Measures microvascular chemistry in the muscle
- Accurate on pigmented skin and obese patients
- Measures pH and muscle oxygenation
- Motion tolerant
Trauma Induced Coagulopathy

- Present upon admission for up to 25% major trauma patients
- Increased risk for
  - Higher transfusion requirements
  - Multiple Organ Failure
  - Longer ICU stay
  - 4X increase in mortality

Who needs a Massive transfusion?

- ABC score (Nunez et al)
  - SBP, HR, FAST, penetrating mechanism, RBC in ED
- McLaughlin score
  - SBP, HR, pH, HCT
- Schreiber score
  - Hgb < 9, INR > 1.5, penetrating injury
- Yucel score
  - SBP, HD, Base deficit, Hgb, Male, FAST, long bone/pelvic fracture

Prehospital FAST

- HEMS service Houston TX
  - 293 pts over 7 months
  - 214 eFAST studies completed
  - Sensitivity 46%, Specificity 94% for intra-abdominal hemorrhage
  - Sensitivity for PTX only 18%
Goals of Resuscitation

- Support until hemorrhage control
- Restore Tissue Perfusion
- Correct coagulopathy
- Prevent hypothermia
- Reduce intracranial pressure?
- Modulation of the Inflammatory Response?

“Damage Control” Resuscitation

Operation Enduring Freedom and Operation Iraqi Freedom – Joint Theatre Trauma Registry

Col JB Holcomb – Head of US Army Institute of Surgical Research

Resuscitation should be prioritized to match principles of Damage Control Surgery

Controlled Resuscitation

“Injection of a fluid that will increase blood pressure carries danger in itself. Haemorrhage in the case of shock may not have occurred to a large degree because the blood pressure is too low, and the flow to scant to overcome the obstacle offered by a clot. If the pressure is raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost.” JAMA 1918
Should we give no fluid?


Limitations to Bickel study

- Penetrating Torso trauma only
- Does not include TBI
- Short transport time in urban setting
- Many protocol violations by EMS
- Delays in OR availability
- Primary endpoint: 24 hour survival

Targeted Resuscitation

- Large bore IV access, IO as alternate
- Titrate fluids
  - Penetrating trauma SBP 80-90 or palp radial pulse
  - Blunt trauma w/TBI target SBP 100-110
- Switch to blood products as early as possible
  - Need to identify patients likely to need a massive transfusion
  - Prioritize rapid transport to trauma facility with surgical capability
PROPPR

- PROPPR: Prospective Randomized Optimal Platelet and Plasma Ratio
- Multicenter clinical trial
- Patients randomized to differing massive transfusion protocols
  - 1:1:1 vs 1:1:2
- Funding from DOD and NIH
- Completed enrollment: 12 sites in the US and Canada, 680 patients

PROPPR study results

- 680 patients enrolled
  - Both groups median 9u PRBC
  - 1:1:1 median 7u plasma vs 1:1:2 5u plasma
  - 1:1:1 median 12 units platelets vs 1:1:2 6 units platelets
  - 24 hr mortality 1:1:1 vs 1:1:2, 12.4 vs 17%, p=0.09
  - 30 day mortality 22.4 vs 26.1%, p=0.25
  - Early exsanguination reduced, 9.2% vs 14.6%, p=0.03
  - Achieved hemostasis: 86% vs 78%, p=0.006
  - No difference in adverse events or complications

JAMA 2015:313:471-482

Prehospital Administration

Blood Products

- Holcomb et al, Prehospital Emergency Care 2014
  - 1677 severely injured patients (792 Ground EMS, 716 Air w/ blood, 169 other air)
- 19% Air patient transfused (blood and plasma)
  - Prehospital transfusion associated with
    - Less acidosis on hospital arrival
    - Decreased use of additional blood products first 24 hrs
    - Decrease in 6 hr mortality but no difference at 24 hrs or 30 days
Houston Prehospital Tranfusion Criteria

- Injured patients > Age 12
- Two or more ABC score points
  - Penetrating truncal injury
  - SBP < 90mmHg
  - HR > 120
  - Positive abdominal FAST
- All patients to receive 1 u plasma and 1 u PRBCs using Buddy Lite warming device

ALNW to participate in PROHS Study

Plasma Options

- Fresh Frozen Plasma
- Liquid Plasma
- Freeze Dried Plasma*
- Lyophylized plasma*

Bottom Line

- Need a well functioning Massive transfusion protocol
  - Rapid delivery of blood products to the bedside
  - Earlier decision to switch from crystalloid to blood products for high risk patients
    - ABC score
    - Early ABG
  - Balanced Resuscitation (1:1:1 is superior)
    - Need to focus on rapid availability of plasma and platelets
    - Prehospital blood products?
Background – Tranexamic Acid

- TXA is an antifibrinolytic
- Prevents breakdown of clot (rather than promoting new clot formation)
- First used in 1966
- Used to control bleeding in many clinical settings:
  - Ruptured intracranial aneurysms, upper GI hemorrhage, hemophilia, pediatric urinary tract surgery, cardiopulmonary bypass, liver transplantation, trauma

Tranexamic acid reduces fibrinolysis

- Tranexamic acid inhibits plasmin and reduces clot breakdown.

Is Fibrinolysis Bad?

- Evidence of fibrinolysis on admission is associated with increased morbidity and mortality
- Shock on arrival and admission hypothermia and high base deficit are predictive of hyperfibrinolysis
- Hyperfibrinolysis is an independent predictor of the need for massive transfusion
Tranexamic Acid

- Anti-fibrinolytic agent
- RCT N=20,211 trauma pts
  - In 274 hospital, 40 countries
  - Loading dose 1 gm over 10 min and then infusion 1gm/8hrs
- Mortality: TXA 14.5%, Placebo 16.0%, RR 0.91

Civilian use of TXA: CRASH-2 Trial

- Results:
  - Mortality reduced in TXA compared to placebo
    - 14.5% vs 16%
  - Relative risk of death (RR) due to hemorrhage based on time of TXA administration after injury:
    - < 1 hour: 5.3% vs 7.7% (RR 0.68 [CI 0.57-0.82])
    - 1-3 hours: 4.8% vs 6.1% (RR 0.79 [CI 0.64-0.97])
    - > 3 hours: 4.4% vs 3.1% (RR 1.44 [CI 1.12-1.84])

Military Use of TXA: Matters study

- MATTERS study (retrospective)
  - 896 patients in a UK combat support hospital who received at least 1 unit PRBC
  - Mortality in patients receiving TXA was 17.4% vs. 24% in those not receiving TXA
  - Patients receiving TXA were more severely injured
  - Increased thrombotic events in TXA group
  - US Joint Theater Trauma System Clinical Practice Guideline for Damage Control Resuscitation now recommends TXA use for any patient requiring blood products
Matters 2

- 1332 patients (retrospective review)
- UK/US military trauma registries, patients receiving at least one unit PRBC, evaluated use of TXA and CRYO
- Logistic regression demonstrated that TXA and CRYO were independently associated with reduction in mortality (OR 0.61, 95%CI: 0.42-0.89)

Cochrane Meta-analyses

- Antifibrinolytics for Peri-operative blood transfusion (elective surgery) 252 RCTs
  - TXA reduced the risk of blood transfusion by 39%, no difference in the risk of reoperation for bleeding or mortality
- Effect of TXA on surgical bleeding, 129 trials
  - TXA reduced the probability of receiving a blood transfusion by 30%
  - Effect on thromboembolic events uncertain, lower mortality

CRASH-2: TBI Cohort Analysis

- Nested within larger trial (10 centers in India & Colombia)
- TBI defined by CT criteria and GCS ≤ 14
- Results:
  - Intracranial hemorrhage progression decreased in TXA vs. placebo
  - Mortality decreased in TXA vs. placebo (10.5% vs. 17.5%)
    - Not statistically significant
    - Small sample size (n = 270)
**TXA in TBI Trial: Thailand**

- RCT (n=240) in isolated moderate to severe TBI
  - randomized to 2 gm TXA bolus vs. placebo
- Results (same as CRASH-2 sub-study):
  - Intracranial hemorrhage progression and mortality decreased in TXA vs. placebo
  - Small sample size
  - Recommendation for larger RCT

**Current Use at HMC**

- TXA indicated for any trauma patient upon activation of the Massive transfusion protocol provided patient within 3 hours of injury
  - 1gm bolus, followed by 1gm infusion over 8 hrs (based on CRASH 2 trial)
- TXA also being adopted for use in OR for cases with high volume blood loss
  - Spine surgery, Pelvic fracture surgery, etc

**What about Prehospital use?**

- PATCH trial: starting now in Australia for hemorrhagic shock
- Pittsburgh trial: multicenter aeromedical study of three dosing regimens for shock
- ROC trial for TBI, now enrolling (Seattle Fire, King County EMS, ALNW)
- ALNW & Whatcom county EMS using it for trauma patients in shock
Specific Aims ROC Trial

- Primary aim: to determine if TXA improves outcome in patients with moderate/severe TBI
  - 6-month GOS-E
- Secondary aims:
  - clinical: DRS, survival, neurosurgical intervention
  - radiographic: intracranial hemorrhage progression
  - safety: seizures, cerebral ischemic events, MI, DVT, PE
- Mechanistic aims:
  - fibrinolysis pathways mediators
  - degree of clot lysis (TEG)

Intervention

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<thead>
<tr>
<th>Bolus with Maintenance</th>
<th>Bolus Only</th>
<th>Placebo only</th>
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<tbody>
<tr>
<td>EMS gives 1 gram TXA bolus</td>
<td>EMS gives 2 gram TXA bolus</td>
<td>EMS gives placebo bolus</td>
</tr>
<tr>
<td>Hospital gives 1 gram TXA over 8 hours</td>
<td>Hospital gives placebo over 8 hours</td>
<td>Hospital gives placebo over 8 hours</td>
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Investigational Invasive Approaches
REBOA: Resuscitative Endovascular balloon occlusion of the aorta

Arsenal’s Device: A Treatment for Non-Compressible, Abdominal Hemorrhage

- Two part liquid injected into body; chemical reaction in the body generates a solid, conformal device
- Foam provides intraabdominal compression to slow or stop hemorrhage
- Delivered using standard access techniques and a delivery device
- Removed at definitive surgery

Foam Appearance and Properties

Duggan et al. J. Trauma 74.6 (2013): 1462-1467.
Efficacy In Lethal Injury Models

Summary of Safety Findings

- Foam was administered in a low-grade spleen injury
- Foam was removed at 3 hours
- Animals were recovered for 28 days and 90 days
- Foam results in focal bowel damage that must be repaired prior to recovery
- All animals at selected dose survived without clinical complications
- No evidence of abdominal compartment syndrome, embolization or sepsis
- Adhesions were not different from control

Delivery Device
Emergency Preservation and Resuscitation (ie Suspended Animation)

- Traumatic Cardiac arrest within 5 minutes of ED arrival
- U Pittsburgh feasibility study
- Aorta cannulated with rapid cooling to 15°C
- Patient taken to the OR and placed on cardiopulmonary bypass and injuries repaired

Gunshot victims to be Frozen in Time

Summary: Internal Bleeding

- Targeted Fluid resuscitation
- Early switch from crystalloid to blood products when available
- TXA within 3 hrs
- Pelvic sheeting
- Drive fast or to OR fast

QUESTIONS?