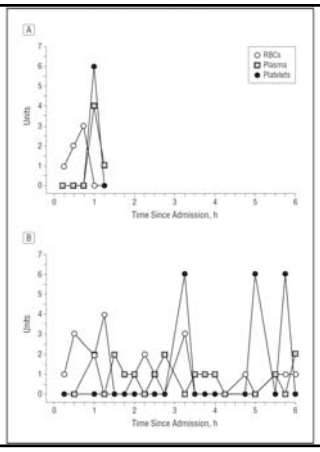
# Ratio Wars

## PROMMTT Study 2013: Background

- Goal: "To relate in-hospital mortality to early transfusion of FFP and/or PLTs and to time-varying FFP:RBC and PLT:RBC ratios
- Prospective, observational cohort study at 10 level I TCs.
- Adult trauma patients, highest level of trauma activation, surviving 30 min. after admission:
  - Received at least 1 unit RBCs within 6 hrs. of admission (n=1245, original study group),
  - Received 3 total units (RBCs, plasma, or platelets) within 24 hours (n=905, the analysis group)
- Main outcome: In-hospital mortality
- "We hypothesized that early transfusion of plasma and platelets in higher ratios would be associated with decreased in-hospital mortality in bleeding patients."

## Ratio Wars: background

- Traditional trauma ratio: crystalloid → pRBCs →other blood products.
- Iraq/Afghanistan experiences: Damage Control Resuscitation (DCR), higher ratios of FFP, PLTs, cryo to RBCs more effective
- The debate begins:
  - Borgman MA. et. al. The Ratio of Blood Products Affects Mortality in Patients Receiving Massive Transfusions at a Combat Support Hospital, *J Trauma* 2007;63: 805-813
  - Kashuk JL., et. al. Postinjury Life Threating Coagulopathy: Is 1:1 Fresh Frozen Plasma: Packed Reb Blood Cells the Answer? J Trauma 2008; 65: 261-271




Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013;148:127–36.

## PROMMTT Study 2013: Results

- FFP:RBC and PLT:RBC ratios were inconsistent for first 24 hrs (both *P*<.001)across trauma centers, within trauma centers, and within a single patient's course of care.
- In the first 6 hours, patients with ratios (FFP: RBC and PLT:RBC) less than 1:2 were 3 to 4 times more likely to die than patients with ratios of 1:1 or higher.
- After 24 hours, plasma and platelet ratios were unassociated with mortality, when competing risks from nonhemorrhagic causes prevailed.

Holcomb JB, Tilley BC, Baraniuk S, et. al. Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma The PROPPR Randomized Clinical Trial *JAMA*. 2015;313(5):471-482. doi:10.1001/jama.2015.12

**Assessment of Blood Consumption (ABC)**

1) Penetrating Trauma (0=no; 1=yes)
2) ED SBP ≤ 90 mmHg (0=no; 1=yes)
3) ED HR ≥120 bpm (0=no; 1=yes)
4) Positive FAST (0=no; 1=yes)

ABC ≥ 2: 75% sensitive, 86% specific predicting MT.

## PROPPR RCT 2015: Background

- Goal: "Compare the effectiveness and safety of a 1:1:1 transfusion ratio of plasma, platelets, and RBCs to a 1:1:2 ratio."
- Phase III trial at 12 Level I trauma Centers.
- August 2012-December 2013.
- Primary Outcome: 24-hour and 30-day-all-cause mortality.
- Prespecified Ancillary Outcomes:
  - Time to hemostasis
  - Blood product volumes transfused
  - Complications
  - Incidence of surgical procedures
  - Functional status.

## PROPPR RCT 2015: Methods-products

- Randomized pre-packed sealed containers to bedside in 10 minutes.
- Rigidly controlled until hemostasis, death, declaration of futility; thereafter no control of resuscitation.

**Table 1**
Contents of container cycles for each ratio group.

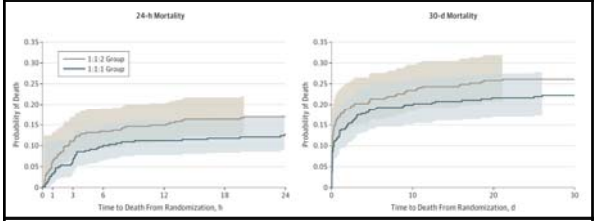
| | | Container 1 | Container 2 |
|---|---|---|---|
| Group 1[a] 1:1:1 | Platelets | 1 | 1 |
| | Plasma | 6 | 6 |
| | RBCs | 6 | 6 |
| Group 2[b] 1:1:2 | Platelets | 0 | 1 |
| | Plasma | 3 | 3 |
| | RBCs | 6 | 6 |

[a] Group 1: Platelets first, then alternate RBCs and Plasma, as clinically required.
[b] Group 2: Platelets first (if available), then alternate 2 RBCs and 1 Plasma, as clinically required.
The container cycles were repeated until hemostasis was achieved and resuscitation completed.

## PROPPR RCT 2015: Methods-patients

- Highest level of trauma activation, received directly from scene.
- Received 1 U of blood component within 1 hour of hospital arrival.
- Predicted by "ABC," or by physician judgment to require MT.
- Initial sample size of 580 to detect a 10% difference in 24-hr mortality, and 12% difference in 30-day mortality.

## PROPPR RCT 2015: Results




- Mortality at 24 hours (12.7%in 1:1:1 group vs 17.0%in 1:1:2 group; difference, −4.2%[95%CI, −9.6%to 1.1%]; *P* = .12).
- Mortality at 30 days (22.4% vs 26.1%, respectivelty, difference, −3.7%[95%CI, −10.2%to 2.7%]; *P* = .26).

## PROPPR RCT 2015: Results

- Exsanguination ↓ in 1:1:1 group (9.2%vs 14.6%; *P* = .03).
- Hemostasis ↑ in 1:1:1 group (86%vs 78%;*P* = .006).
- Despite more FFP (median of 7U vs 5U, *P* < .001), PLTs (12 U vs 6 U, *P* < .001) and similar amounts of red blood cells (9 U) in 1:1:1 over the first 24 hrs., no differences in 23 prespecified complications (including ARDS, MOF, VTE, sepsis, transfusion related comps).
- Laboratory-guided "catching up" after controlled, ratio driven products occurred in 1:1:2, such that cumulative ratios approached 1:1:1.

## Neal MD, et. al. When a little goes a long way: Background

- Despite multiple studies FFP/PLTS/CRYO:PRBCs ratios, little research on crystalloid:pRBC ratio appropriate in Massive Transfusion.
- Hypothesis: An increased crystalloid PRBC (C:PRBC) ratio would be associated with increased morbidity and poor outcome after MT.
- Primary outcomes interest: in-house mortality, Nosocomial infection (NI), Multi-organ failure (MOF), Acute Respiratory Distress Syndrome (ARDS), Abdominal Compartment Syndrome (ACS)
- 7 institutions, Nov 2003-October 2008

## PROPPR RCT 2015: Conclusion

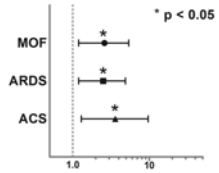
***"Given the lower percentage of deaths from exsanguination and our failure to find differences in safety, clinicians should consider using a 1:1:1 transfusion protocol, starting with the initial units transfused while patients are actively bleeding, and then transitioning to laboratory-guided treatment once hemorrhage control is achieved."***

## Neal MD, et. al. When a little goes a long way: Results

- 1710 blunt injured patients, 452 enrolled (required MT and survived beyond 24 hrs); mean ISS=34.
- Cohort's median transfusion/1st 24 hrs.: 17 L crystalloid; 16u pRBCs; 8.4u FFP; 1.6u PLTs .
- Overall in-hospital mortality : 22.6%; MOF: 63.5%; NI: 56.2%; ARDS: 36.3%; ACS: 15.1%.
- Importantly, as C:PRBC ratio increased, volume of blood component transfusion significantly decreased.

Neal MD, Hoffman MK, Cuschieri J, Minei JP, Maier RV, Harbrecht BG, Billiar TR, Peitzman AB, Moore EE, Cohen MJ, Sperry JL. Crystalloid to packed red blood cell Transfusion ratio in the massively transfused patient: When a little goes a long way. *J Trauma.* 2012;72: 892–898

## Neal MD, et. al. When a little goes a long way: Results




Independent OR for C:PRBC ratio > 1.5:1

- Regression analysis revealed that a C:RBC ratio of >1.5:1 increased the following Odds Ratios:
  - MOF: OR, 2.6; 95% CI, 1.2–5.4; *p* =0.011
  - ARDS: OR, 2.5; 95% CI, 1.2– 4.9; *p* 0.010
  - ACS: OR, 3.6; 95% CI, 1.3–9.7; *p* 0.009

## Neal MD, et. al. When a little goes a long way: Results

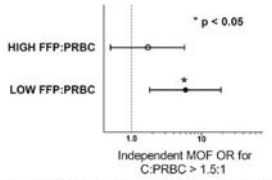



Figure 3. Independent ORs associated with infusion of crystalloid in a ratio >1.5:1 relative to PRBCs and the development of MOF stratified high and low FFP:PRBC ratios.

- The independent risk of MOF associated with a C:PRBC ratio 1.5:1 was strongest, significant, and most pertinent to patients who received a low FFP:PRBC ratio (OR=5.9; 95% CI, 1.8 –19; *p* =0.003),

## WHOLE BLOOD BACKGROUND

- Whole Blood (WB) has been the traditional transfusion product in trauma since WWII
- Component therapy introduced in 1960s-70s
- WB resurfaces as "ideal" resuscitation product during subsequent military conflicts
- OIF/OEF
  - >10,000 U WB transfused to US Personnel to date.
  - Series of articles emerge heralding WB use in trauma

## Neal MD, et. al. When a little goes a long way: Conclusion

- "These results suggest that high-volume crystalloid and low-volume FFP resuscitation may create a worst case scenario and identify a patient cohort and resuscitation strategy at particularly elevated risk for MOF."
- "It may be that in the absence of aggressive treatment of the early coagulopathy postinjury, the risk of crystalloids promoting an excessive inflammatory response is accentuated."
- "Similarly, obviating FFP resuscitation with crystalloid resuscitation may overwhelm the already primed innate immune response and results in higher organ failure and poor outcome." inflammatory system is tipped over the edge

*Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, Holcomb JB, The Early Whole Blood Investigators.* A Randomized Controlled Pilot Trial of Modified Whole Blood versus Component Therapy in Severely Injured Patients Requiring Large Volume Transfusions. *Ann Surg* 2013;258:527–533

# WHOLE BLOOD

## Cotton BA, et. al. RCT trial mWB vs. CT: Background

- Single-center, randomized pilot trial, primary outcome: 24-hour transfusion volume
- Primary Outcome: 24-hr. transfusion volumes
- Sponsored by the Department of Defense
- Hypothesis: "…resuscitation of severely injured patients with modified whole blood (mWB) would result in fewer overall transfusions compared with component (COMP) therapy."

## Cotton BA, et. al. RCT: mWB vs. CT: Methods

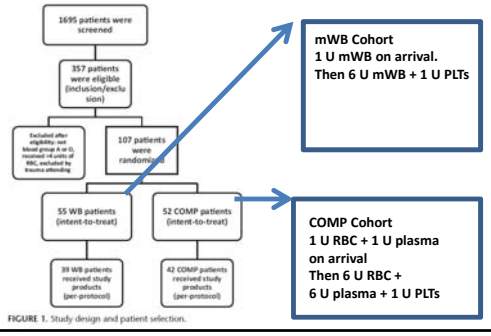
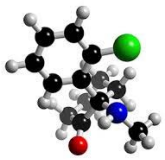


FIGURE 1. Study design and patient selection.

# Ketamine




## Cotton BA, et. al., RCT: mWB vs. CT

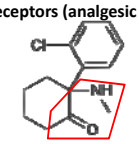
- **1° outcome: WB not superior to CT in blood product utilization.**

| | WB Group (n = 33) | COMP Group (n = 34) | *P* |
|---|---|---|---|
| Median 24-hr RBC transfusions, U | 4 (2, 6) | 6 (2, 13) | 0.02 |
| Median 24-hr plasma transfusions, U | 4 (2, 7) | 6 (2, 14) | 0.02 |
| Median 24-hr platelet transfusions, U | 0 (0, 1) | 1 (0, 2) | 0.09 |
| Median 24-hr total transfusions, U | 11 (5, 17) | 16 (4, 41) | 0.02 |
| 24-hr mortality, % | 6% | 9% | 0.62 |
| 30-d mortality, % | 6% | 9% | 0.62 |

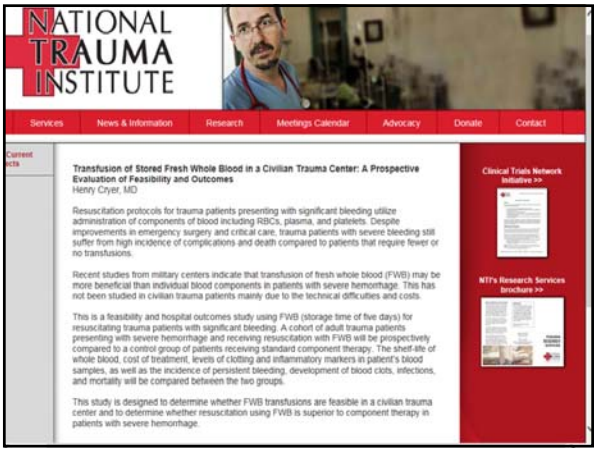
- **Sensitivity analysis (patients without severe TBI) use of mWB significantly reduced transfusion volumes.**

## Ketamine

- **Phencyclidine derivative: NMDA receptor antagonist, also binds opioid mu & sigma receptors (analgesic & anesthetic)**




- **pKa of 7.5, ~50% dissociated @ pH 7.45; 12% bound to plasma proteins (rapid blood-brain equilibration & clinical onset)**
- **Developed by Parke-Davis in 1962; safer anesthetic than phencyclidine**
- **Recreational street drug: "K," "Special K" and "Vitamin K" (made Schedule III drug in 1999)**
- **Raises ICP? Strictly an OR drug?**




# Ketamine and ICP

4. **Effect on ICP.** During spontaneous ventilation, ketamine produces an increase in $Paco_2$ and ICP, in both the presence and absence of pre-existing intracranial hypertension. Increases in ICP might also occur in the presence of normoventilation. Interestingly, ketamine is a noncompetitive *N*-methyl-D-aspartate antagonist. In one animal model of incomplete cerebral ischemia, ketamine was shown to reduce cerebral infarct size. In the clinical arena, however, ketamine is still avoided in most neurosurgical patients, particularly those who have mass lesions and the potential for increased ICP.

**Benzodiazepines**

1. **Effect on CBF and CMRo.** Benzodiazepines

Lippincott Williams & Wilkins

## Zeiler, et. Al. Ketamine on ICP in TBI: results

- In some neurosurgical/neuroanesthesia literature, same four studies are cited as evidence for urge caution using ketamine in neurologically ill:
  - Wyte SR, Shapiro HM, Turner P, Harris AB. Ketamine-induced intracranial hypertension. Anesthesiology. 1972;36(2):174–6.
  - Shapiro HM, Wyte SR, Harris AB. Ketamine anesthesia in patients with intracranial pathology. Br J Anaesth. 1972;44:1200–4.
  - Gardner AE, Olson BE, Lichtiger M. Cerebrospinal fluid pressure during dissociative anesthesia with ketamine. Anesthesiology. 1971;35(2):226–8.
  - List WF, Crumrine RS, Cascorbi HF, Weiss MH. Increased cerebrospinal fluid pressure after ketamine. Anesthesiology. 1972;36(1):93–4.
- All four studies focus on ketamine as a dissociative anesthetic for elective neurosurgical procedures (mainly shunt revisions).
- Few actual patient cases described; those described showed post-ketamine ICP elevation measured via ventricular or lumbar catheter.
- Proposed mechanism: large vessel vasodilation vs. small vessel

**Ketalar**
(Ketamine Hydrochloride Injection, USP)

Because pharyngeal and laryngeal reflexes are usually active, Ketalar should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

Resuscitative equipment should be ready for use.

*The incidence of emergence reactions may be reduced* if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

**Information for Patients**
As appropriate, especially in cases where early discharge is possible, the duration of Ketalar and other drugs employed during the conduct of anesthesia should be considered. The patients should be cautioned that driving an automobile, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more (depending upon the dosage of Ketalar and consideration of other drugs employed) after anesthesia.

**Drug Interactions**
Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

## Zeiler, et. Al. Ketamine on ICP in TBI: results and conclusion

- 7 articles: 156 patients (101 adults 55 pediatric), varying doses of ketamine
  - 4 articles compare ketamine vs. opiate infusions: all 4 found no difference in ICP/fluctuations, equal sedative properties
  - 3 articles focus on bolus ketamine to prevent ↑ICP during stimulus or to ↓ICP during acute elevation: all 3 studies cited trend toward ↓ICP with ketamine bolus, and sustained effect when used pre-emptively for stimulating procedures.
- Authors make an "Oxford 2b," and "GRADE C" that ketamine does not lead to a elevation in ICP in severe TBI, in the setting of an intubated and sedated patient.

**Zeiler FA, et. al. The Ketamine Effect on ICP in Traumatic Brain Injury. Neurocrit Care (2014) 21:163–173**

## Ketamine in the Prehospital Setting


| Patient | Injury | TQ | IV | Dose (mg) | Additional Dose (mg) | Total (mg) | Midazolam (mg) | Dilaudid (mg) | OTFC | Morphine (mg) | Pain Before | Pain After | PTSD | Additional Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | LE shrapnel | 4 | Y | 75 / IV | 60 / IV | 135 / IV | 2 / IV | n/a | n/a | 12 / IV | 10 | 0 | No | Limb movement, hallucinations |
| 2 | GSW UE | 2 | Y | 50 / IV | 50 / IV | 100 / IV | n/a | 2 / IV | 1 | n/a | 9 | 4 | No | Cannot recall the all of the incident after ketamine |
| 3 | BLE Amp | 4 | Y | 75 / IV | 50 / IV | 125 / IV | 2 / IV | n/a | n/a | n/a | 9 | 0 | No | Recall after ketamine, moved extremities, incoherent speech |
| 4 | LE Amp | 1 | Y | 75 / IV | 50+50 / IV | 175 / IV | 2 / IV | n/a | n/a | n/a | 10 | 0 | No | Cannot recall incident after ketamine |
| 5 | BLE/UE shrapnel | 3 | Y | 75 / IV | n/a | 75 / IV | n/a | n/a | 1 | n/a | 9 | 0 | Yes | No recollection |
| 6 | GSW UB/LE | 1 | Y | 100 / IV | n/a | 100 / IV | n/a | 2 / IV | 1 | n/a | 10 | 4 | No | Hallucinations |
| 7 | GSW abdomen | 0 | Y | 20 / IV | 20/ IV | 40 / IV | 7.5 / IV | n/a | 1 | 15 / IV | 10 | 4 to 5 | No | Was 10/10 until receiving ketamine |
| 8 | Facial shrapnel | 0 | N | 100 / IM | 100 / IM | 200 / IM | n/a | n/a | n/a | 23 / IV | 8 | 0 | Mild | Mild hallucinations CONUS |
| 9 | Fall, femur fracture | 0 | Y | 200 / IM | 25 / IV | 225 / IV-IM | n/a | n/a | 1 | n/a | 10 | 0 | No | Analgesia allowed femur manipulation, no TBI noted |
| 10 | GSW chest | 1 | Y | 50 / IV | 50+25 / IV | 125 / IV | n/a | n/a | n/a | n/a | No further data available | | | |
| 11 | GSW LE | 1 | N | 250 / IM | n/a | 250 / IM | 2.5 / IV | n/a | n/a | n/a | | | | |
| Avg. | | | | 65 / IV, 183 / IM | 42 / IV, 100 / IM | 87 / IV, 217 / IM | 3.2 | 2 | | | | | | |

Notes: Amp = amputation; BLE = bilateral lower extremity; CONUS = contiguous United States; GSW = gunshot wound; IV = intravenous; LE = lower extremity; n/a = not applicable; OTFC = oral transmucosal fentanyl citrate; PTSD = posttraumatic stress disorder; UE = upper extremity.
*Pain scale 0–10, with 0 = no pain, 10 = worst pain.

**Fisher AD. Prehospital Anealgesia with Ketamine for Combat Wounds: A Case Series. Journ Spec Ops Med Vol 14 Ed.4/Winter pp. 11-17.**

## Fisher AD, et. al. Prehospital Ketamine for Combat Wounds: Results

- ***"The extremity movement made it difficult to move a patient through heavy brush and the incoherent speech was above the normal volume of speech, however, it is not known if it caused unnecessary attention from the enemy…"***
- ***"One patient developed a period of apnea after receiving ketamine and midazolam…the move was made more difficult by the sporadic gunfire from the enemy and suppressive fire from attack helicopter; the patient was moving his extremities throughout this time…"***

## Fisher AD, et. al. Prehospital Ketamine for Combat Wounds: Background

- **TCCC (10/2013) ketamine : for "casualty unable to remain in the fight:"**
  - **50-100 mg IM /50 mg IN; Q 30-60 min (until pain controlled or nystagmus)**
  - **If IV/IO access, 20 mg slow push, repeat Q 5-10 min**
- **2009: 75th Ranger Regiment (75RR) implements ketamine protocol that exceeds TCCC recommendations (RMHB 4th edition):**
  - **Basic Pain Management Protocol:**
    - **1st line: Oral Transmucosal Fentanyl Citrate (OTFC)**
    - **2nd line: ketamine 250 mg IM vs. morphine 10 mg IV vs. hydromorph 2 mg IV.**
  - **Advanced Pain Management Protocol**
    - **1st Line: OTFC**
    - **2nd line: midazolam 2mg w/ketamine 75 mg IV/IO followed by 20-25 mg increments OR Ketamine 250 mg IM**
- **Retrospective analysis of 75RR's PHTR 1/09- 10/14 for ketamine use at the POI**

## Fisher AD, et. al. Prehospital Ketamine for Combat Wounds: Conclusion

- **"Ketamine appears to be a safe and effective as a dissociative agent and an analgesic in the prehospital setting."**
- **"It has a superior safety profile when used in a combat trauma setting, with none of the undesirable side effects of opioids."**
- **"It is recommended that the US FDA authorize the use of ketamine for analgesia."**

# Thromboelastography (TEG)

Holcomb JB, et. al. Admission Rapid Thrombelastography Can Replace Conventional Coagulation Tests in the Emergency Department. *Ann Surg* 2012;256: 476–486.

## Thromboelastography: background

- TEG first described in 1948 by Dr. Hellmut Hartert of Heidleburg, has been used to evaluate coagulation profiles for >60 years
- 1967, Hardway, et. al. uses TEG to describe coagulation changes seen in combat casualties in Vietnam.
- Rapid TEG (rTEG) uses tissue factor instead of kaolin, further speeding reaction and clot formation

## Holcomb JB, et. al. Admission rTEG vs. CCT, 2012: background

- Single Center, retrospective cohort study
- September 2009-February 2011
- Both CCTs (PT, PTT, INR, PLT, fibrinogen) and rTEG obtained on all trauma patients upon arrival
- 1974 patients enrolled
- Hypothesis: "rTEG would provide more useful and cost-effective evaluation of the coagnulation system than multiple CCTs"

## Holcomb JB, et. al. Admission rTEG vs. CCT, 2012: results

- When controlling for age, injury mechanism, weighted-revised Trauma Score, base excess and hemoglobin:
  - ACT predicted RBC transfusion.
  - α-angle predicted massive RBC transfusion better than PT/aPTT or INR ($P < 0.001$).
  - α-angle was superior to fibrinogen for predicting plasma transfusion ($P < 0.001$).
  - MA was superior to PLT for predicting platelet transfusion ($P < 0.001$).
  - LY-30 documented fibrinolysis.
- These correlations improved for transfused, shocked or head injured patients.
- The charge for r-TEG ($317) was similar to the 5 CCTs ($286).

| Laboratory Values | Blood Product Transfusion |
|---|---|
| ACT > 128 | Plasma and RBCs |
| *r*-value > 1.1 | Plasma and RBCs |
| k-time > 2.5 | Cryoprecipitate / fibrinogen / plasma |
| $\alpha$-angle < 56 | Cryoprecipitate / fibrinogen / platelets |
| MA < 55 | Platelets / cryoprecipitate / fibrinogen |
| LY30 > 3% | Tranexamic acid |
| PT > 18.0 | Plasma |
| aPTT > 35 | Plasma |
| INR >1.5 | Plasma |
| Platelet count < $150 \times 10^9$/L | Platelets |
| Fibrinogen < 180 g/L | Cryoprecipitate / fibrinogen |

# Questions?

## Trauma Anesthesia Society

- **Founded in 2011**
- **Over 200 members**
- **Access to monthly Newsletter containing updates in research, literature reviews, and society news**
- **Access to Trauma Anesthesia Digest**
- **Active membership: $100, associate membership is $75, residents are $25.**