

Traumacology: Drugs for the Trauma Bay

Session Overview

Trauma resuscitations frequently necessitate timely medication administration. This session will explore two potentially controversial resuscitation drugs, tranexamic acid (TXA) and ketamine. Should we be giving TXA to our patients with trauma-related hemorrhage? Is it safe to administer ketamine for rapid sequence intubation in patients with potential traumatic brain injury? In addition to addressing these two critical questions to provide application for bedside clinical practice, we will also highlight some more uses for ketamine in the trauma patient.

Objectives

1. Review the evidence behind the use of TXA in both major and minor trauma patients.
2. Discuss the physiologic effects of ketamine.
3. Discuss the current literature to support using ketamine in trauma patients for sedation and pain relief.

Tranexamic Acid (TXA)

1. MOA: TXA inhibits fibrinolysis by forming a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. It also inhibits the proteolytic activity of plasmin. [Lexicomp 2018]
 - a. Theory: Blood clots in trauma patients and up to 60% of trauma patients may have massive underlying lysis
 - b. There are over 70 RCTs evaluating TXA for non-traumatic bleeding (overall benefit)
2. Pertinent trials
 - a. CRASH-2 ([Lancet 2010;376:23-32](#))
 - i. Design
 1. Multi-center RCT in 274 hospitals (40 countries)
 2. Over 20,000 pts randomized to receive TXA or placebo
 - ii. Results
 1. All-cause mortality: TXA (1463 [14.5%]) vs. placebo (1613 [16.0%]; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035). **ARR 1.5% = NNT 67**
 2. Risk of death due to bleeding was significantly reduced (4.9% vs 5.7%; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077). **ARR 0.8% = NNT 125**
 - iii. Criticisms
 1. Didn't measure anything to do with clotting or injury severity score [Small sample size of hypotensive (SBP < 90 mm Hg) (31.5%) and tachycardic (HR>107) (48%) patients which were the target populations]
 - a. Response: Pragmatic trial design so more patients could be enrolled. This design minimizes variability in results. 99% follow up. A simple 2-page enrollment form was used. - BUT, not necessarily generalizable to advanced trauma system

2. Uncertainty principle was used to enroll patients. Treating clinicians enrolled patients in whom the benefit of TXA was unknown.
 - a. Response: Allowed for clinical equipoise > minimized ethical issues involved with assigning patients to different treatment arms.
3. More than half of the patients didn't receive blood products
 - a. Response: Many of the countries in which patients were enrolled did not have blood products available - BUT, not necessarily generalizable to advanced trauma system
4. Giving a clotting drug will increase thrombotic events
 - a. Response: There was no difference in clotting events - BUT, probably because they were not actively sought in many of the participating hospitals
- b. [Lancet 2011;377:1096-101](#)
 - i. Subanalysis of CRASH-2 trial focused on time to TXA administration
 - ii. Early treatment (≤ 1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5.3%] events in TXA group vs 286/3704 [7.7%] in placebo group; relative risk [RR] 0.68, 95% CI 0.57–0.82; $p < 0.0001$). **ARR 2.4% = NNT 42**
 - iii. Treatment between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4.8%] vs 184/2996 [6.1%]; RR 0.79, 0.64–0.97; $p = 0.03$)
- c. [Roberts, BMJ 2012](#)
 - i. Subanalysis of CRASH-2 patients according to baseline risk of death
 - ii. No heterogeneity in effect of TXA on all cause mortality ($P = 0.96$ for interaction) or deaths from bleeding ($P = 0.98$) by baseline risk of death. No heterogeneity in effect of TXA on risk of thrombotic events ($P = 0.74$). Can be given to all severities.
- d. MATTERS ([Morrison, Arch Surg 2012](#))
 - i. Design - Retrospective observational study comparing TXA with no TXA in military combat patients (Afghanistan) receiving ≥ 1 unit of PRBCs
 - ii. Results
 1. The TXA group had lower unadjusted mortality than the no-TXA group (17.4% vs 23.9%, respectively; $P = .03$) **despite being more severely injured** (mean ISS, 25.2 vs. 22.5, respectively; $P < .001$). Benefit greatest in group who received massive transfusion (14.4% vs 28.1%, $p = .004$), where TXA was also independently associated with survival (odds ratio = 7.228; 95% CI, 3.016–17.322) and less coagulopathy ($P = .003$).
- e. MATTERS II ([Morrison, JAMA Surg 2013](#))
 - i. Expanded sample size of MATTERS I study to 1,332 patients (identified from prospectively collected UK/US trauma registries) who required ≥ 1 RBC units.
 - ii. Despite greater ISSs and RBC transfusion requirements, mortality was lowest in patients who received TXA (18.2%) or TXA/CRYO (11.6%) compared with CRYO alone (21.4%) or no-TXA/CRYO (23.6%).
- f. [Cole, Ann Surg 2015](#)

- i. Prospective cohort of severely injured pts (ISS >15) at civilian trauma system
 - ii. Patients receiving TXA (n = 160) were more severely injured, shocked, and coagulopathic on arrival. TXA independently associated with reduction in MOF [OR = 0.27, CI: 0.10-0.73, P = 0.01] and protective for adjusted all-cause mortality (OR = 0.16 CI: 0.03-0.86, P = 0.03) in shocked patients.
 - g. [Valle, J Trauma Acute Care Surg 2014](#)
 - i. TXA associated with increased mortality, but TXA pts were sicker than the placebo group, and overall ISS was higher than even the MATTERS trial
 - ii. Authors attributed to early fluids and OR availability
 - h. [Harvin, J Trauma Acute Care Surg 2015](#)
 - i. 1,032 trauma patients with hyperfibrinolysis defined as LY-30 of 3% or greater.
 - ii. 98 (10%) received TXA, and 934 (90%) did not. TXA patients were more severely injured (median ISS, 29 vs. 14), had a lower blood pressure, and were more likely to be in shock (median, base excess, -5 mmol/dL vs. -2 mmol/dL).
 - iii. Unadjusted in-hospital mortality was higher in the TXA group (40% vs. 17%, p < 0.001). There were no differences in venous thromboembolism (3.3% vs. 3.8%).
 - iv. TEG shows whether pattern of clot formation or breakdown is normal or not. Pathological hyperfibrinolysis does not occur in all trauma patients. So, a normal TEG doesn't exclude that TXA may have benefit since it is thought to work by changing the normal balance
 - i. Prehospital administration ([El-Menyar, Am J Emerg Med 2018](#))
 - i. Effect of TXA on 24-hour mortality had a pooled odds ratio (OR) of 0.49 (95% CI 0.28-0.85), 30-day mortality OR of 0.86 (95% CI, 0.56-1.32), and thromboembolic events OR of 0.74 (95% CI, 0.27-2.07).
 - j. [PATCH trial](#) underway in Australia - aims to determine the effects of early administration of tranexamic acid on survival and recovery of severely injured patients treated within advanced trauma systems
3. Acquisition cost ~ \$17 for 1 gm
 4. Contraindications
 - a. Subarachnoid hemorrhage (from package insert)
 - b. Risk/benefit with thrombosis or thromboembolism (TEG or ROTEM might be helpful)
 5. When to consider using TXA ([J Trauma Acute Care Surg 2013](#); [Ker, Cochrane Database Syst Rev. 2015](#))
 - a. Adult trauma patients with severe hemorrhagic shock (SBP < 90 mm Hg) who are at risk for bleeding (ie, cross-matched or receiving blood)
 - b. Only administer TXA if less than 3 hours from time of injury
 - c. TXA administration: 1 g IV over 10 minutes, then 1 g IV over 8 hours

Ketamine

1. MOA: NMDA receptor antagonist that blocks glutamate. Low doses produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance. [Lexicomp 2018]
2. ICP Myths
 - a. ICP increases were described in the Neurosurgery/Neuroanesthesia literature primarily in patients with CSF outflow obstruction undergoing elective neurosurgical procedures.

Recent data support use in ED and ICU patients, even potentially with TBI ([Zeiler, Neurocritical Care 2014](#); [Chang, CNS Neuroscience & Therapeutics 2013](#); [Cohen, Ann Emerg Med 2015](#))

- i. [Bar-Joseph G, J of Neurosurg Pediatr 2009](#)
 1. 82 administrations to 30 children with intracranial hypertension.
 2. Following ketamine administration, ICP decreased by 30% (from 25.8 +/- 8.4 to 18.0 +/- 8.5 mm Hg) ($p < 0.001$) and CPP increased from 54.4 +/- 11.7 to 58.3 +/- 13.4 mm Hg ($p < 0.005$).
- b. Findings from these reviews:
 - i. The use of ketamine in a controlled ventilation setting and in combination with other sedative agents has demonstrated no increase in ICP.
 - ii. An association between the degree/duration of hypotension and neurologic outcomes in patients with TBI has been established. Therefore, clinicians generally avoid induction agents that cause or may exacerbate preexisting hemodynamic instability such as opioids, propofol, or benzodiazepines.
 - iii. Data on ketamine and outcomes are sparse in this specific population
3. RSI
 - a. Only induction agent that has both sedative and analgesic properties
 - b. Common dose: 1.5 mg/kg
 - c. [May consider lower dose in shock patients](#)
4. Pain (adapted from Dr. Josh Farkas' PulmCrit blog)
 - a. Low dose infusions (e.g. 0.1-0.3 mg/kg/hr) may provide analgesia with minimal side-effects. Combining ketamine and PRN opioids could provide a baseline level of analgesia while reducing the opioid requirement. Ketamine also appears to prevent opioid tolerance and hyperalgesia, which would be helpful among patients ventilated for longer periods of time ([Joly, Anesthesiology 2005](#); [Visser, Biomed Pharmacother 2006](#))
 - b. The side effect of greatest concern is delirium, which can occur at intermediate subdissociative doses of ketamine. At very low doses (e.g. 0.12 mg/kg/hr), the risk of psychiatric side-effects is minimal, with the ketamine level falling into the analgesic-dose range ([Jouguelet-Lacoste J, Pain Med 2015](#); [Forero, Pain Pract 2012](#))
 - c. Ketamine 0.2 mg/kg comparable to morphine 0.1 mg/kg at 15 min ([Mahshidfar, Anesth Pain Med 2017](#))
5. EtOH withdrawal
 - a. In addition to the downregulation of GABA receptors in chronic ethanol users, there is an upregulation in NMDA receptor subtypes. Although the pathophysiology is much more complex, when ethanol abstinence occurs, there is a shortage of GABA-mediated CNS inhibition and a surplus of glutamate-mediated CNS excitation. If GABA agonists are the mainstay of treatment, why not also target the NMDA receptor? Enter ketamine.
 - b. There are now three studies evaluating ketamine in severe ethanol withdrawal ([Wong, Ann Pharmacother 2015](#); [Pizon, Crit Care Med 2018](#); [Shah, J Med Toxicol 2018](#)). They

were covered in detail on [Academic Life in EM](#). Ketamine has the potential to serve as a great partner to our GABA agents in the management of severe ethanol withdrawal.

- i. Unlike dexmedetomidine, which does not target the underlying pathophysiology, ketamine does attack part of the root cause. Therefore, a reduction in benzodiazepines may be an appropriate endpoint with ketamine (but not for dexmedetomidine).
- ii. All 3 published studies were retrospective and not controlled. This needs to be taken into account when considering ketamine. However, the 2018 Pizon study reported on meaningful, patient-oriented outcomes like ICU length of stay and intubations. While well-designed trials are needed, ketamine seemed to be effective with few reported adverse effects in both studies.
- iii. The infusion rate used in two studies was approximately 0.2 mg/kg/hr and seems to be a good place to start if considering ketamine for this indication. A bolus up to 0.3 mg/kg may be considered for some patients. The 2018 Shah study used a much higher infusion rate. More studies are needed but I'm glad to see we're starting to look at it.

6. Sedation

- a. Ketamine is gaining traction as a prehospital (and ED) option for managing severe agitation or excited delirium syndrome. Two prospective studies add information that may help delineate ketamine's role in this setting. ([Cole, Clin Toxicol 2016](#); [Isbister, Ann Emerg Med 2016](#))
- b. Ketamine can be used as a primary sedative agent or as a rescue agent.
- c. Intubation rate has been as high as 39% after prehospital ketamine, but may potentially be reduced by lower doses ([O'Connor, Prehosp Emerg Care 2018](#))
- d. Anecdotally, we start with 2–3 mg/kg IM and repeat if necessary after 5 min. Most patients have not required a second dose and none have been intubated. This allows time to place an IV line and initiate additional treatment. ([Hayes, Clin Toxicol 2016](#))

7. Concentrations

- a. Available as 10 mg/mL (20 mL), 50 mg/mL (10 mL), and 100 mg/mL (5 mL).
- b. Having more than one concentration available, specifically in the ED, could lead to medication errors; the 100 mg/mL concentration is most appropriate for IM administration, while the lower concentrations are more appropriate for most other ketamine indications when given IV.

8. Contraindications

- a. Conditions in which an increase in blood pressure would be hazardous
- b. Note: In the ED, these additional absolute contraindications exist from ACEP guidance [[Green, Ann Emerg Med 2011](#)]:
 - i. Infants <3 months of age
 - ii. Known or suspected schizophrenia (even if currently stable or controlled with medications)