

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 a 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. It also inhibits the proteolytic activity of plasmin. [Lexicomp 2016]
 - 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) - <http://www.ncbi.nlm.nih.gov/pubmed/20554319>
 - 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, didn't measure injury severity score
 - 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.
 2. The uncertainty principle was used to enroll patients. Treating clinicians enrolled patients in whom the benefit of TXA was unknown.
 - a. Response: This allowed for clinical equipoise which minimized ethical issues involved with assigning patients to different treatment arms of the trial.
 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

- 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
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;74:1575-86) (Ker K, et al. Cochrane Database Syst Rev. 2015 May 9;(5):CD004896)
 - 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 2016]
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.
 - i. Zeiler F, et al. Neurocritical Care 2014;21(1):163-73.
 - ii. Chang LC, et al. CNS Neuroscience & Therapeutics 2013;19(6):390-5.
 - iii. Cohen L, et al. Ann Emerg Med 2015;65(1):43-51.
 - iv. Bar-Joseph G, et al. J of Neurosurg Pediatr 2009;4(1):40-6.
 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 (<http://emcrit.org/podcasts/intubation-patient-shock/>)
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 V, et al. *Anesthesiology* 2005;103:147-55.) (Visser E. *Biomed Pharmacother* 2006;60:341-8.)
 - 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, et al. *Pain Med* 2015;16:383-403.) (Forero M, et al. *Pain Pract* 2012;12:154-8.)
5. EtOH withdrawal
- a. BACKGROUND
 - i. In addition to down regulation of GABA receptors in chronic ethanol users, there is an upregulation of NMDA receptors. When ethanol abstinence occurs, there is a shortage of GABA-mediated CNS inhibition and a surplus of glutamate-mediated CNS excitation.
 - b. THE DATA
 - i. Just one retrospective study exists of 23 patients (Wong A, et al. *Ann Pharmacother* 2015;49(1):14-9.). Mean initial infusion dose and median total infusion rate were 0.21 and 0.20 mg/kg/h, respectively. The median change in BZD requirements at 12 and 24 hours post-ketamine initiation were -40.0 and -13.3 mg, respectively. The mean time to AWS resolution was 5.6 days. There was one documented adverse reaction of oversedation, requiring dose reduction.
6. Sedation
- a. Ketamine is gaining traction as a prehospital (and ED) option for managing severe agitation or excited delirium syndrome. Two new prospective studies add information that may help delineate ketamine's role in this setting. (Cole JB, et al. *Clin Toxicol.* 2016 Apr 21. Epub ahead of print.) (Isbister GK, et al. *Ann Emerg Med* 2016;67:581-7.)
 - 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.
 - 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 BD. *Clin Toxicol.* 2016;54:545-6.)
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 SM, et al. *Ann Emerg Med* 2011;57:449-61]:
 - i. Infants <3 months of age
 - ii. Known or suspected schizophrenia (even if currently stable or controlled with medications)