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Traumacology: Drugs for the Trauma Bay

Session Overview

Trauma resuscitations frequently necessitate timely medication administration. This session will explore two resuscitation medications, 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.

Virtual ACEP Questions

1. In which clinical scenario should tranexamic acid be considered?
    a. Traumatic brain injury
    b. Trauma with hypotension and suspected bleeding [Explanation: The subset of trauma patients most likely to benefit from TXA are those with hypotension secondary to suspected bleeding.]
    c. All trauma patients
    d. Traumatic arrest patients
2. Which of the following contraindications for ketamine has been largely disproven by newer data?
    a. Infants < 3 months old
    b. Schizophrenia
    c. Elevated intracranial pressure [Explanation: The 2011 ACEP clinical practice guideline for ED ketamine dissociative sedation lists choices A and B as contraindications. Elevated ICP is no longer a contraindication based on newer literature demonstrating either no effect on ICP or, in some cases, a decreased ICP with ketamine.]
    d. Conditions in which an increase in blood pressure would be hazardous

Tranexamic Acid (TXA) in Trauma

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)
    i. Design
        1. Multi-center, double-blind, placebo-controlled, randomized trial in 274 hospitals (40 countries)
        2. Over 20,000 pts randomized to receive TXA or placebo
    ii. Primary outcome: All-cause mortality within 4 weeks of injury
    iii. Inclusion - adult trauma patients, significant hemorrhage (SBP < 90 or HR >110 or both), at risk of significant hemorrhage, within 8 hours of injury
    iv. 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**
        3. Patients with SBP < 75 had largest benefit
    v. Limitations
        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. 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
        3. 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
    vi. Strengths
        1. Good blinding and use of intention to treat
        2. Funders not involved in any aspect of study
        3. Applicable in real world due to lack of laboratory testing
b. Subanalysis of CRASH-2 (Lancet 2011)
    i. 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**
    ii. 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. MATTERs (Morrison 2012)
    i. Design - Retrospective, observational, single-center 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).
2. Include chart from REBEL EM everything that bleeds

d. MATTERS II (Morrison 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%).

e. CRASH-3 (Lancet 2019) (*adapted from REBEL EM summary*)
i. Design: Randomized, placebo-controlled trial done in 175 hospitals in 29 countries with > 9,000 TBI patients treated within 3 hrs of injury (GCS ≤ 12 with no CT evidence of extracranial bleeding)
ii. Primary outcome: Head injury-related death in hospital within 28 days of injury in patients treated within 3 hours of injury
iii. Results
1. 12,737 patients (9,202 treated within 3 hours)
2. Risk of head injury-related death: TXA 18.5% vs placebo 19.8% (RR 0.94, 95% CI 0.86-1.02)
a. Subgroup that may have benefit is mild-to-moderate head injury (GCS 9-15). Death was reduced (RR 0.78, 95% CI 0.64-0.95)
3. Risk of vascular occlusive events was similar in both groups
iv. Limitations
1. Wide CIs, did not meet pre-specificed enrollment
2. 97% of patients had SBP > 90
3. Risk of DVT/PE probably an underestimate since they were only diagnosed when positive on imaging or post-mortem
v. Discussion
1. Pooled data from this trial + previous shows small benefit
2. In mild-to-moderate GCS, earlier treatment reduced head injury-related mortality within the first 24 hours but not afterward (patients may have died due to non-bleeding related mechanisms)
a. Importantly, all cause mortality was not reduced at any time point
3. Should we change practice based on secondary endpoints?

f. Prehospital administration (El-Menyar 2018, Rowell 2020)
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).

ii. PATCH-Trauma 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 (Napolitano 2013; Ker 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) **or** adult patients with mild-to-moderate TBI with ICH on head CT
        i. Notably, TXA did not reduce mortality in patients with non-traumatic ICH (Sprigg 2018)
    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

Tranexamic Acid (TXA) in PPH

The WOMAN trial (Lancet 2017) (*adapted from REBEL EM summary*)

1. Design
    a. Randomized, double-blind, placebo-controlled trial, of > 20,000 women ≥16 years of age with post-partum hemorrhage after vaginal delivery or caesarean section from 193 hospitals in 21 countries
    b. Uncertainty principle - patients excluded if clearly would be beneficial or would not be beneficial
    c. Same bolus dose as CRASH-2, could be repeated
2. Primary outcome - changed during the trial, but before data analysis
    a. Original: Composite outcome of all-cause mortality and/or hysterectomy within 42 days of giving birth
    b. Final: Death from PPH
3. Results
    a. Death reduced in patients given TXA (1.5% vs. 1.9%, p=0.045) with larger benefit if given within 3 hours. **NNT = 250**
    b. No difference in thrombotic events
4. Limitations
    a. Uncertainty principle could underestimate the benefit of tXA in PPH
    b. Primary endpoint was altered after initiation of the trial
    c. Diagnosis of PPH made clinically and no assessment of inter-rater reliability in making this determination
5. Take-Home Point - TXA may be beneficial, but NNT is high and fragility index is 0

Meta-Analysis of CRASH-2 and WOMAN Trial (Gayet-Ageron 2018) (*adapted from REBEL EM summary*)

What They Did: Pooled data from 2 large RCTs

Outcomes: Absence of death from bleeding

Results:

- 40,138 patients. In total there were 3,558 total deaths in both studies. 1,408 (40%) of deaths were due to bleeding and 884 of these deaths (63%) occurred within 12 hours of onset.
- TXA Increased Overall Survival from Bleeding
    - TXA: 96.6% vs Placebo: 96.0% (ARR: 0.6%; NNT = 167; OR 1.20; 95% CI 1.08 – 1.33; p = 0.001)
- No Increase in Vascular Occlusive Events with TXA
    - TXA: 0.2% vs Placebo: 0.3% (OR 0.73; 95% CI 0.49 – 1.09)
- Effect of Treatment Delay on Survival

Treatment Delay (Min)	TXA	Placebo	OR (95% CI)	NNT
0 - 60	1.7%	2.2%	1.26 (0.96 - 1.66)	---
60 - 120	3.9%	5.8%	1.53 (1.27 - 1.84)	53
120 - 180	3.8%	5.3%	1.42 (1.09 - 1.83)	67
180 - 240	3.2%	3.5%	1.08 (0.76 - 1.54)	---
240 - 300	4.3%	2.9%	0.67 (0.45 - 0.98)	---
300 - 360	4.4%	3.6%	0.80 (0.51 - 1.27)	---
360 - 420	4.0%	3.2%	0.78 (0.48 - 1.28)	---
420 - 480	3.0%	2.1%	0.70 (0.35 - 1.39)	---

Limitations: Exact onset time of bleeding unknown. In CRASH-2 this may have underestimated the effectiveness of TXA and in WOMAN this may have potentially overestimated the effectiveness of TXA as time of birth was used as the onset of bleeding.

Take Home Points:

1. TXA reduces mortality in patients with massive bleeding from trauma or PPH
2. Give TXA as soon as bleeding is suspected
3. Thrombotic events were not increased, but also weren't necessarily looked for (and we know adverse events are under-documented).

<u>Ketamine</u>

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 2014, Chang 2013, Cohen 2015, Torres 2020)

i. Bar-Joseph 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 and recent data suggests ketamine doesn't have less hypotension in RSI compared to etomidate (April 2020)
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 2005, Visser 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 2015, Forero 2012)
   c. Ketamine 0.2 mg/kg comparable to morphine 0.1 mg/kg at 15 min (Mahshidfar 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 2015, Pizon 2018, Shah 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 2016, Isbister 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 high rate is multifactorial and might be reduced by lower doses (O'Connor 2019)
    d. We start with 2 mg/kg IM (max 200 mg) 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 2016, O'Brien 2020)
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 2011]:
        i. Infants <3 months of age
        ii. Known or suspected schizophrenia (even if currently stable or controlled with medications)