

Clinical Practice Management Guidelines

Antifibrinolytic Therapy Suggested Algorithm for Administration of TXA

I. Purpose

To describe the data, physiology and use of antifibrinolytics in acute severe trauma injury.

II. Statement of the Problem

Acute coagulopathy of trauma is associated with hyperfibrinolysis in patients with severe traumatic injuries. These factors occur independently of hypothermia and acidosis but combine to contribute to a very high mortality rate. In conjunction with efforts to optimize the resuscitation of the traumatically injured patient, damage control procedures and utilization of a massive transfusion protocol to achieve an optimal transfusion ratio, the use of antifibrinolytic agents and purified coagulation factors has been used in an attempt to improve outcomes. Tranexamic acid (TXA) is the latest studied antifibrinolytic agent which has been used in the care of the trauma patient.

TXA is a synthetic version of the amino acid lysine and blocks plasminogen from interacting with fibrin and reduces the breakdown of clot. It was initially developed as a treatment for reduction in bleeding in dental extractions in hemophiliacs. It has subsequently been used in multiple other procedures, arthroplasty, transplant, cardiac surgery, and other surgeries. It has been suggested as an adjunct in the treatment of bleeding caused by trauma.

This guideline will look at the data available regarding the use of this drug in the trauma patient. Discussion will include:

- A. What is the clinical effectiveness of TXA?
- B. What patients are appropriate candidates to receive TXA?
- C. What is the appropriate timing of administration of TXA?
- D. What is the appropriate dosing of the medication to achieve optimal results?

III. Recommendations with Scientific Background

- A. What is the clinical Effectiveness of TXA?

1. Level I Data

CRASH-2, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage trial, was a randomized prospective placebo controlled clinical trial which looked at 20,211 patients from 274 hospitals in 40 countries.

- TXA administration reduces all-cause mortality was reduced in the groups receiving the drug from 16% to 14.5%.
- Benefit highest in the severe shock group with SBP < 75mmHg reducing mortality from 35.1% to 30.6%.
- TXA administration reduced risk of death from bleeding from 5.7% to 4.9%.
- TXA has no impact on TBI outcomes and there is no increased risk of vascular occlusive events.

2. Level 2 Data

The MATTERS study, Military Application of TXA in Trauma Emergency Resuscitation, is a retrospective observational study looking at combat casualty patients treated in Afghanistan.

- TXA patients had lower unadjusted mortality than the no-TXA cohort, 17.4% vs 23.9% (p=0.03).
- The TXA group was more severely injured, ISS 25.2 vs 22.5 (p<0.001).
- There was no increased risk of DVT or PE.

MATTERs II Study – expanded the sample size of the previous data set to look at outcomes.

- Despite greater ISSs and RBC transfusion requirements mortality was lowest in patients who received TXA or TXA and Cryoprecipitate compared to Cryoprecipitate alone or neither.
- TXA alone 18.2%; TXA and Cryo 11.6%; Cryo alone 21.4%; neither TXA or Cryo 23.6%.

3, Level 3 Data

Cochrane Systematic Reviews

- TXA reduced the risk of blood transfusion by 39%, but did not reduce the need for reoperation due to bleeding or mortality.
- TXA reduced the probability of receiving a blood transfusion by 30%.

TXA has been shown in large multicenter randomized clinical trials as well as in military application cohort study to have a significant reduction in mortality in critically injured patients.

B. What patients are appropriate candidates for administration of TXA.

Level I data – administration of TXA in Adult patients with significant hemorrhage, systolic blood pressure (SBP) <90 and/or heart rate >110, presentation within 8 hours of injury.

Level 2 data – TXA should be used as part of the resuscitation from severe injury with hemorrhage and/or mass transfusion requirement or the presence of hyperfibrinolysis.

Level 3 data – Prognostic study Kutcher et al, identified factors which are highly predictive of hyperfibrinolysis that would warrant consideration of empiric treatment.

The CRASH-2 trial inclusion criteria were adult patients with significant hemorrhage, SBP < 90mmHg and/or heart rate >110 and presentation within 8 hours of injury to the treating hospital.

The MATTERS study retrospective review identified the patients to receive TXA as those determined to be severely injured by the treating clinician. At later times during the study TXA was given by protocol to those patients requiring emergency blood products or those with evidence of hyperfibrinolysis on thromboelastogram.

Kutcher et al, describe a series of patients with critical injuries who had blood sent on arrival for prognostic correlation to help determine factors which would predict hyperfibrinolysis to direct empiric therapy. The presence of hypothermia (temperature <36.0C), acidosis (pH <7.2), relative coagulopathy (INR >1.3 or PTT >30), or relative thrombocytopenia (platelet count <200) identified hyperfibrinolysis with 100% sensitivity and 55.4% specificity.

C. What is the appropriate timing of administration of TXA

Level I data – TXA should be administered as early as possible. Ideally it should be administered less than three hours from injury. Administration after between three and eight hours of injury can worsen outcomes.

Level 2 data – No significant new recommendations

Level 3 data – No significant new recommendations

In the CRASH II trial there is strong data to demonstrate earlier TXA administration is associated with improved effect. In patients receiving TXA within 1 hour of injury there was a 32% (p<0.0001) reduction in risk of death from bleeding. TXA given greater than one hour and less than three hours from injury reduced death due to bleeding compared to placebo by 21% (p=0.03) In patients who received the TXA between three and eight hours there was an increase in bleeding associated death compared to placebo 44% increase. The MATTERS study did not make any comments on timing of administration of TXA.

D. What is the appropriate dosing of the medication to achieve optimal results?

Level 1 data – CRASH 2 used 1g over 10 minutes IV and an additional 1g given over 8 hours

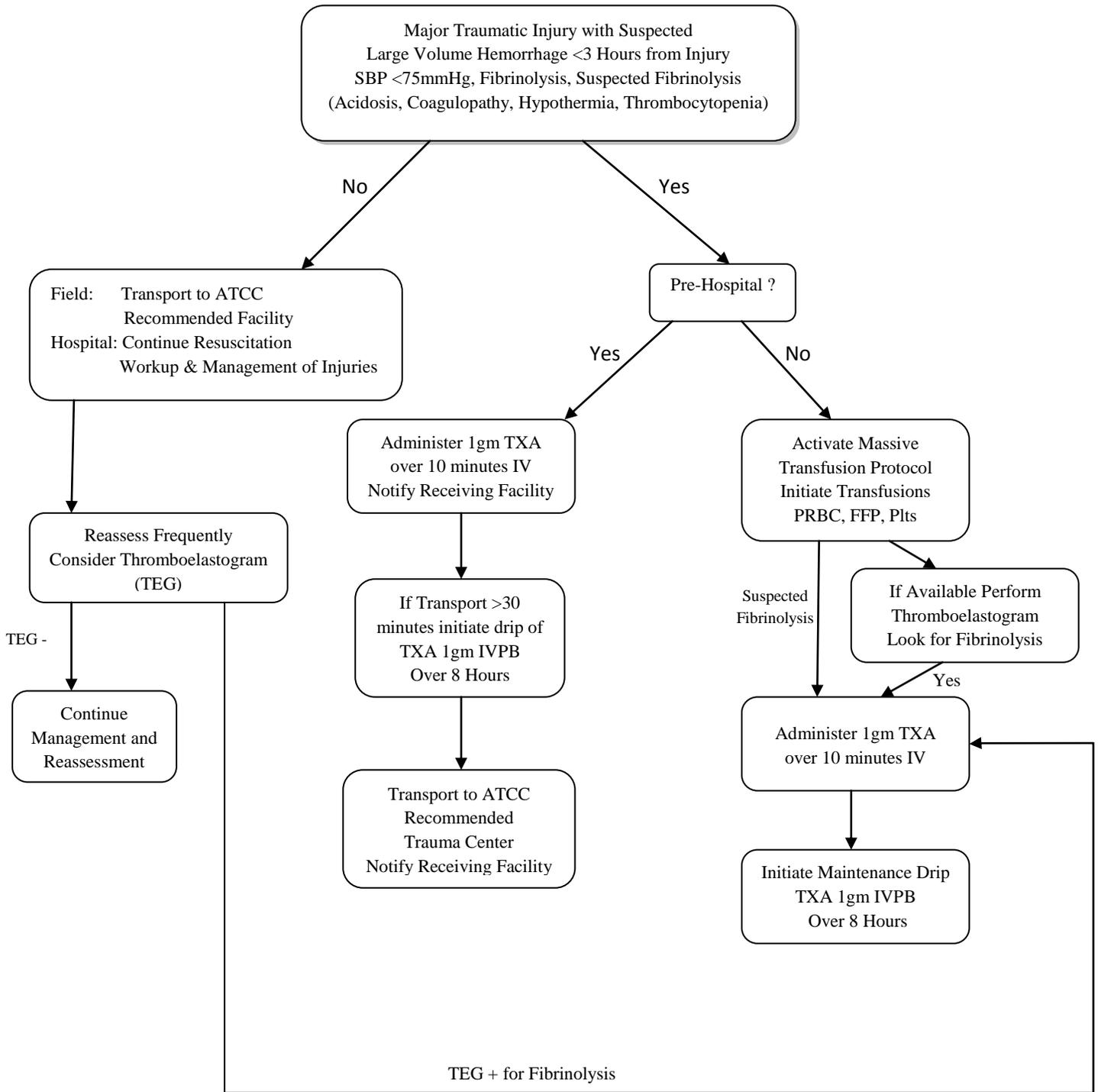
Level 2 data – MATTERs used 1g administered IV bolus at repeated at the discretion of the managing clinician.

Level 3 data – no recommendations

There is no currently available evaluation of the efficacy of different dosing regimens of TXA in trauma. The two studies listed above demonstrate different dosing algorithms both with good outcomes. There is no data to specifically recommend one regimen over the other.

IV. Conclusions

- A. TXA administration in adult trauma patients should be limited to severe hemorrhagic shock with systolic blood pressure ≤ 75 or known hyperfibrinolysis on TEG or predictors of fibrinolysis such as hypothermia ($t < 36.0$), acidosis ($\text{pH} < 7.2$), thrombocytopenia (plts < 200) or coagulopathy (INR > 1.3 or PTT > 30)
- B. Only administer TXA if less than 3 hours from time of injury.
- C. TXA should be administered 1gm IV over 10 minutes IV in 100cc of NS then 1 gm IV in 1000cc of LR over 8 hours
- D. Initial administration may occur in the field if there is coordination between the EMS agency and the receiving facilities to ensure that there is availability of maintenance infusion dose at the receiving facility.



Bibliography

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