Author's response to reviews

Title: A prospective, randomized, double-blinded single-site control study comparing blood loss prevention of tranexamic acid (TXA) to epsilon aminocaproic acid (EACA) for corrective spinal surgery

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Author's response to reviews: see over
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Dear Reviewers,

You comments for the following submitted manuscript (citation below) were appreciated and well received. We have attached a revised version of the manuscript with a point by point response to the reviewers concerns as well.

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A prospective, randomized, double-blinded single-site control study comparing blood loss prevention of tranexamic acid (TXA) to epsilon aminocaproic acid (EACA) for corrective spinal surgery Kushagra Verma, Thomas J Errico, Kenneth M Vaz and Baron S Lonner

The topic is relevant, and no study of this topic of comparable rigor exists in the literature. The protocol is concise and well-written and without major flaws. I have several minor comments:

1. More details regarding administration of the antifibrinolytic agents should be included in the standardized treatment protocol. When is the infusion started? At incision? Before? When is the infusion terminated? Is it intraoperative only?

The infusion is started 15 minutes prior to incision. The infusion is given in two parts. First a loading dose is given over 15 minutes at a volumetric rate of 20 ml/hour for a 50 kg patient. Following the initial loading dose, a maintenance dosage is given at one-tenth of the loading dose or 2 ml/hour for a 50 kg patient for the duration of the procedure and discontinued at closure. This volumetric rate is adjusted accordingly for the patient’s body weight. The volume infused remains constant regardless of whether the patient is receiving TXA, EACA, or saline. TXA is administered at 10 mg/kg hr for a loading dose followed by 1 mg/kg hr for a maintenance dose. In contrast, EACA is administered at 100 mg/kg hr for a loading dose, followed by 10 mg/kg hr for a maintenance dose. To adjust for this difference, the pharmacy is instructed to prepare the EACA at a tenfold higher concentration (250 mg/ml) than the TXA (25 mg/ml). The TXA and EACA treatments are both prepared in saline and both treatment preparations are visually indiscernible from saline alone. The loading and maintenance doses for TXA and EACA used in the protocol are in accordance with recent literature citing efficiency and safety at these dosages. 7, 8, 10-14

2. I am concerned about blinding the clinicians caring for the patient in the postoperative period with respect to whether the patient had been administered antifibrinolytics or placebo. If the former, the clinicians suspicion for related complication such as stroke or renal failure may be higher, and this may lead to alteration in care. At a minimum, this ethical consideration merits further discussion.

While clinicians are blinded to the patient’s particular treatment group, at any time during surgery or in the post-operative period any clinician can be “unblinded” to the patient’s treatment group if there is a concern for a complication. In addition, all patients are followed daily by the residents and fellows on the spine service and will also be followed by spine research fellows caring for the patient. The research residents also record and document basic metabolic profile
(BMP) and complete blood count (CBC) lab values daily. The research fellows pay careful
attention to the blood creatinine and blood urea nitrogen/creatinine ratio (BUN/Cr) monitoring
daily for possible renal failure. Sequential compression devices (SCD) are given to all spine
patients and they are encouraged to mobilize out of the hospital bed on post-op day 2. Spine
patients are closely monitored for signs of a DVT by the medicine attending physicians and
nurses caring for patients. A copy of the consent form is placed in every chart in addition to a
list of contact numbers of research persons involved with the study. There is also a note on the
front cover of the chart informing all nurses and physicians that the patient is enrolled in the
study with contact information for the research fellows and for the pharmacy department. The
pharmacy is instructed to release the treatment group for any patient if requested by medical
personnel caring for the patient or a spine research fellow.

With regards to complications, to date there has been no clear association between the use of
antifibrinolytics, such as TXA and EACA, and renal failure or thrombosis. A similar
medication with anti-fibrinolytic properties, aprotinin, did lose FDA approval over concerns
regarding renal failure in cardiac patients and the theoretical risk of thrombosis. Aprotinin
functions as a serine protease inhibitor. In contrast, TXA and EACA are synthetic lysine analogs
that act as inhibitors of fibrinolysis. This difference in mechanism most likely accounts for the
lack of association between the use of antifibrinolytics and renal failure. Regardless, patients
in the study are carefully monitored for signs of renal failure post-operatively. Any patient with
an elevated or rising creatinine is carefully followed by resident and attending orthopaedic
surgeons, internal medicine physicians, and the research fellows. If the elevation in creatinine is
suspicious for renal failure, patients will be “unblinded” and treated appropriately.
Complications will be diligently recorded and reported in the final manuscript.

> 3. The authors do not discuss complications of antifibrinolytics to any meaningful degree in
this protocol, and they should. In the study design, the authors should specifically outline how
they intend to monitor for and identify complications of the antifibrinolytics.

This point should be addressed in the above point.

> Furthermore, additional discussion should be added regarded the potential complications of
treatment - ultimately, the decision on whether use of these agents is warranted is based not only
on utility in reducing blood loss, but comparing this utility to complications of the treatment
itself.

As mentioned above, TXA and EACA, are synthetic lysine analogs that bind to and produce a
structural change in plasminogen preventing conversion of plasminogen to plasmin and
conversion of fibrinogen to fibrin. These drugs therefore have a dual mechanism of
anticoagulation: decreased fibrinolysis and decreased platelet aggregation due to the inactivation
of plasmin. TXA and EACA have been used most in cardiac surgery and meta-analysis has
clearly shown a reduction of intra-operative blood loss and allogenic transfusion rate with these
medications. While there have been concerns that use of these medications may lead to an
increased risk of MI, DVT, or renal failure; there has been no clear evidence suggesting an
increased risk. Other side effects that have been reported have been minor including
headache, upset stomach, flushing, and hypotension. Considering the reported reduction in
operative blood loss and allogenic transfusion rate in both the cardiac and spine literature, the benefits of treatment outweigh the potential side effects. While these medications are widely used, they are currently not the standard of care in spinal surgery. This study aims to delineate the benefits of TXA versus EACA in spinal surgery, which may help to identify the patients most in need of this treatment.