Author’s response to reviews

Title: Efficacy of tranexamic acid in reducing blood loss in posterior lumbar spine surgery for degenerative spinal stenosis with instability: a retrospective case control study

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Author’s response to reviews: see over
Dear ladies and gentlemen,

enclosed you’ll find the revised manuscript with required changes as recommended by the reviewer Jean Wong and Leah Y Carreon. The revisions made are marked red in the manuscript. The format is now according to the journal style.

I look forward to hear from you soon.

Best regards

Stefan Endres
Comments to the reviewer: Leah Y Carreon

In general, all revisions made are marked red in the present manuscript. Required minor essential revisions are revised. Copy edit was done by BioMedEs. (www.biomedes.co.uk)

Major compulsory revisions

- What method was used to determine which patients received tranexamic acid?
  Added to the method section. “The control group had undergone the lumbar spinal fusion procedure in 2009 before tranexamic acid use was introduced into our institution and consisted of 51 patients. The tranexamic acid group included 46 patients, enrolled in 2010, who received 1g tranexamic acid intravenous preoperative (60 min before surgery) and six hours and twelve hours postoperative, based on the study by Zohar et al. [11].”

- PLIF performed over all levels?
  Revised in method section. “Posterior lumbar interbody fusion was performed over one to three levels and in all cases a posterolateral bone graft was done. The bone graft for fusion (posterolateral fusion) was a mixture of Endobone® and autologous bone obtained from the decompression procedure. No iliac crest bone graft harvesting was performed on all patients over at least 3 levels. The average number of posterior instrumented levels was 4.8 (range 4–5).”

- Demographics for each group?
  Extended information is now given in table 1.

- Actual p values in both tables?
  Added to table 2.

- Explanation why the results are different from those previously published?
  Discussion has been rewritten. “But why are these findings contrary to published data showing that antifibrinolytic agents have a positive effect in major orthopedic and spine surgery? Heterogeneous patient populations (adolescent scoliosis, neuromuscular scoliosis, acquired degenerative instability, etc.), differences in surgical techniques (anterior, posterior, anterior-posterior, lumbar and cervical), heterogeneity in the doses and type of antifibrinolytic agent, timing of administration, and a lack of standardized dose regimens and transfusion thresholds may help to explain why the results of the present study are different from those previously published, which showed differences in blood loss and transfusion between patients who received tranexamic acid and those who did not.
  Elwatidy et al. reported on the efficacy and safety of a large dose of tranexamic acid in spine surgery [9]. They enrolled 64 patients of whom 18 had multilevel anterior cervical discetomies, 22 had decompressive surgery for multisegmental stenosis, 15 had laminectomy and posterior instrumentation and nine had laminectomy and resection of a spinal tumor. The heterogeneity of this study population makes it difficult to compare the results because these procedures entailed more or less significant blood losses.
  Another study by Baldus et al. compared the safety and efficacy of aprotinin and tranexamic acid in controlling blood loss during lumbar pedicle subtraction osteotomy
(PSO) in adults [22]. The main difference from the present study is that the surgical procedure of PSO is substantially more complex and entails greater blood loss (mean 1114 ml – 2260 ml) than decompressive surgery with interbody fusion and instrumentation.

Colomnia et al. performed a retrospective case control study to determine the impact of aprotinin or tranexamic acid use on reducing intraoperative blood loss and transfusion needs in complex spine surgery. They enrolled patients with diagnoses of adult scoliosis, neuromuscular scoliosis, congenital scoliosis, degenerative lumbosacral disease and posttraumatic kyphosis. The surgical procedures were varied and included posterior instrumented fusion, anterior instrumented fusion, anterior plus posterior instrumented fusion, posterior lumbar interbody fusion (PLIF), pedicle subtraction osteotomy and Smith-Peterson osteotomy. The authors found that the duration of surgery was the main predictive factor of total blood loss among the patients [23].

In conclusion, the present authors presume that the duration of the surgical procedure and type of surgery are predictive factors for significant blood loss and transfusion requirement in spine surgery. It is likely that tranexamic acid use results in a greater reduction in blood loss and transfusion the longer the surgical procedure lasts and therefore the greater the blood loss is.”

- Limitations of this study?
  Added to the discussion section. See last paragraph.
  “Although we conducted a retrospective case-control study and the possibility of the results being affected by recall bias due to historical controls cannot be ruled out, the study provides evidence that the use of tranexamic acid in posterior lumbar spine surgery is not always necessary. But the strengths of this study are the homogenous patient population in both groups, and the fact that the surgery was performed by a single surgeon.”

**Minor compulsory revisions**

- Abstract / Background, Sentence 4:1: Blood loss as major complication deleted.
- Background / Introduction is now on a single page.
- Methods, 1st paragraph: No iliac bone graft was harvested. See page 4 line 14.
- Statistical analysis section has been rewritten.
- The first two sentences in the result section has been deleted.
- The 4th and 5th paragraph in the discussion section has been deleted.
Comments to the reviewer: Jean Wong

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Abstract:
- Background: Indicate clearly the purpose of the study.
  The background has been revised and the aim of the study was defined. “This study was done to evaluate the efficacy of tranexamic acid in reducing blood loss in spine surgery”

- Results: Actual blood loss with mean and SD and red cell transfusions and complications should be added.
  This information has been added to the results section in the abstract.

Background:
- Expected blood loss?
  Usually we (in our department) expect a blood loss of 1-2 red cell units. But up to my knowledge there is no literature that states the expected blood loss for the conducted surgery. Looking at the most recent literature regarding tranexamic acid use and spine surgery no one mentioned an expected blood loss because of different types of surgery. Therefore i’m not sure how to mention and is it really necessary to mention?

- Erythropoetin?
  No one received erythropoetin. It has been deleted from the manuscript.

Methods:
- Inclusion and exclusion criterias?
  Added to methods section. “All patients were in need of spinal fusion surgery of 4 to 5 segments owing to degenerative spinal stenosis with instability. Exclusion criteria were renal dysfunction identified by a glomerular filtration rate lower than 50 ml/min, current use of anti-coagulant medication, any history of coronary artery disease with stent placement and history of thromboembolic events.”

- Period of time
  Added to the method section. “Between January 2009 and December 2010, we enrolled 97 patients who were to have a posterior lumbar spine surgery in this retrospective case control study.”

- Average age with SD?
  Added to the method section. “The tranexamic acid group comprised 31 males and 15 females, mean age 67 years (SD: 10.5); in the control group there were 27 males and 24 females with a mean age of 69 years (SD: 9.8).”

- Rationale for dose of tranexamic acid and time of first dose?
  Added to the method section. “The control group had undergone the lumbar spinal fusion procedure in 2009 before tranexamic acid use was introduced into our
institution and consisted of 51 patients. The tranexamic acid group included 46 patients, enrolled in 2010, who received 1g tranexamic acid intravenous preoperative (60 min before surgery) and six hours and twelve hours postoperative, based on the study by Zohar et al. [11].”

- Preoperative autologous blood donation?
  None of the patients had a preop autologous blood donation. It is not offered in our institution because it was shown to be not cost effective in orthopedic surgery and it has a higher frequency of transfusion because of a lower preop hemoglobin concentration.

- Measuring intraop blood loss?
  This was done by the use of a cell saver system. The volume was determined before reprocessing the drainage volume.

- Criteria for transfusion?
  Added to the method section. “The established practice in our department is that patients are transfused if postoperative hemoglobin is < 8mg/dl in patients with no coronary heart disease, or < 10mg/dl in patients who have coronary heart disease and physiological signs of inadequate oxygenation.” Co-morbidities like history of cardiovascular disease were not mentioned because they led to exclusion. See above.

- Adverse effects of tranexamic acid?
  Added to method section. “Furthermore, the numbers of red cell transfusions were assessed, and complications such as suspected medication or allergic reaction, suspected myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism and renal failure were analyzed.”

Results:
- Fluid administered?
  In our hospital the fluids of choice for spine surgery are crystalloids. This was added to table 2.

- Reference for table 1?
  Added to page line 29.

- Amount of blood transfused?
  Each patient who was in need of a transfusion received 2 Units of red cells.

- Report of Complications?
  Added to the result section (page 6 line 24-26) and table 2.

Discussion:
- First paragraph revised. A short introduction and aim of the study is given. Then the results are summarized. “Among patients undergoing major orthopedic and spine surgery, antifibrinolytic agents compared to placebo reduce bleeding, reduce the risk of transfusion and do not appear to increase the risk of myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism. [8,12,13,14,15,16,17,18,19]. These observations are consistent with those found in the cardiovascular surgery literature [20,21].
The aim of the present study was to evaluate the efficacy of tranexamic acid in reducing blood loss and the need for allogenic blood transfusion in patients undergoing posterior lumbar spine surgery. Our results demonstrate no significant reduction in blood loss or allogenic blood transfusion with the use of tranexamic acid. No adverse events with the use of tranexamic acid were seen in our population. But why are these findings contrary to published data showing that antifibrinolytic agents have a positive effect in major orthopedic and spine surgery?

- Limitations of the study?
Added at the end of the discussion. Limitations and strengths of the present study are mentioned.