Author's response to reviews

Title: The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery.

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Author's response to reviews: see over
The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery.


I am pleased to send you a revised version of our manuscript entitled “The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery”.

We have modified the manuscript in accordance to the suggestions received, where appropriate. Principally, we have incorporated data on blood losses as rightly requested by one of the reviewer and yourself. We have however not switched our primary endpoint from the number of unit of blood product transfused to the amount of blood loss and have explained why in the manuscript. We understand you may decide to reject the manuscript on that basis but prefer to stand with our views, based on our understanding of the literature and expert’s views in the field.

We have answered each of the point raised in this document, and made changes accordingly in the manuscript.

We thank the reviewers for their report and argumentation.

Yours sincerely,

Alain Vuylsteke.
1. Reviewer's report

Mark Ereth

Reviewer's report:
General
I am comfortable with the changes made by the authors and agree with publication.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
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Discretionary Revisions (which the author can choose to ignore)

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2. Reviewer's report
Valter Casati

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) The fact that the Mangano’s study has been published after the submission of the authors’ article is not sufficient to justify the avoidance of its citation in the Bibliography.

It seems not so difficult to added it in the paper without to change in a substantially manner the paper, for example in the Discussion. Seen the important discussions raised by the publication of the Mangano’s paper, it is easy to foretell that in the future all the literature on antifibrinolytic drugs use in cardiac surgery will have the start point from the article published on The New England Journal of Medicine.

Furthermore, more recent, another very important article, similar in the structure and in the conclusions of the Mangano’s paper, has been published by Karkouti et al on Transfusion (March 2006 pages 327-338), accompanied by an Editorial written by Jerrold H Levi. In my opinion the authors cannot totally ignore so important new information. In general, it is a precise duty of the authors to render the readers, particularly those less expert, “able to amalgamate” the information of the literature.

We recognize the importance of the papers by Mangano et al and Karkouti et al, that were published subsequently to our submission. We have now added references to these, as well as various editorials, comments and subsequent publications:

In the introduction:

We therefore decided to investigate the impact of tranexamic acid administration on the use of red blood cells and other blood products using the data collected prospectively in our hospital from 30/10/00 to 21/09/04. This reports comes at a time when the safety of aprotinin is reviewed in light of recent evidence suggesting that aprotinin may have a major negative impact on outcome and that alternatives drugs, such as tranexamic acid, may not only be cheaper but also safer alternatives [15, 16]. Aprotinin is an antifibrinolytic agent whose efficacy on decreasing perioperative transfusion has been extensively and rigorously documented [17] and concerns on its safety has indeed prompted numerous reactions [17-20].

and discussion:

This study does not suggest that tranexamic acid is a safer alternative to other antifibrinolytic, neither does it address the possibility that it may affect morbidity as recently reported with aprotinin [16-20].

2) I understand that a new statistical analysis may be expensive for the authors, justifying the maintenance of the original analysis of the data (with all the intrinsic limits and bias which the authors must clearly address). What I don’t understand, and I consider erroneous, is the affirmation of the authors regarding the fact that the propensity score may be applied only in studies considering larger numbers of covariates.

I do apologize for the erroneous statement I made in relation to propensity score and was dully corrected by one of our co-author (FC) who is an MRC-statistician. The issue of the

The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery. Comments to reviewers - 3
The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery.

Comments to reviewers - 4

Selection of statistical tests is discussed in more details to the answers given to the comments made by the next reviewer as they answer this point as well.

3) It is totally unclear to me how, reading a paper having as argument the use of an anti-hemorrhagic drug, the readers may be “distracted” by a simple datum such as perioperative bleeding. It is not for “the reviewer benefit” (sic!) that the authors must report this important information in their paper!

We have added this information to the paper, as well as conducted statistical tests of the obtained data. As expected, blood loss is significantly decreased by the administration of tranexamic acid. The reviewer is probably well aware that a statistically significant reduction in blood loss may not translate in a significant reduction in transfusions and return to theatre in practice. Statistical analysis may turn a small difference that is clinically insignificant and not affecting clinical practice into a highly significant one in statistical terms, mainly when analyzing a high number of patients. Moreover, an increased blood loss will only be relevant if it indeed increases the need for transfusion and alter outcomes.

The changes made include:

Abstract: The administration of tranexamic acid also significantly decreased blood loss.

Methods: Another outcome measure was added on request of the Journal Editor, asking whether the administration of tranexamic acid decreased blood loss.

Results: The analysis of blood loss showed that the median (IQR) total blood loss was 575 mL (375, 875) in the NTA group compared to 450 mL (325, 675) in the TA group, a highly significant difference (p<0.0001 Mann-Whitney test). Corresponding figures for 12 hours blood loss are 450 mL (300, 675) in the NTA group compared to 350 mL (250, 500) in the TA group (p<0.001). Total blood loss for patients returned to theatre was 1959 mL (1444, 2925) for those patients receiving tranexamic acid compared with 2000 mL (1550, 2675) for those not receiving tranexamic acid (a non significant difference). In contrast, a highly significant difference (p<0.001) in total blood loss was observed in those patients not returned to theatre when comparing the ones who had received tranexamic acid (TA group: 425 mL (325, 625)) compared with the ones who did not (non TA group: 550 mL (375, 775)).

An univariate analysis of these data showed that a reduction in blood loss of 21% was expected in the TA compared to the NTA group. This analysis also indicates with high statistical significance (all p<0.001) that postoperative blood loss is greater in males, those undergoing non-elective surgery, those undergoing CABG or CABG and valve surgery (compared to just valve surgery), those receiving aspirin or clopidogrel, older patients, patients with a high BMI, high Euroscore or long bypass time. The subsequent multivariate modelling indicated that a reduction in blood loss of 24% is expected in the TA compared to the NTA group.

Discussion: The administration of tranexamic acid indeed significantly reduced the amount of blood loss. Interestingly, this difference was identified for the whole population and the patients who did not return for re-exploration, but not significant for those patients who were taken back to theatre.
Other statistically significant differences were observed in relation to postoperative blood loss, but some of the highly significant differences were small due to the large sample size (i.e. the median blood loss for patients receiving clopidogrel was 500 mL compared with 450 mL for those patients not receiving clopidogrel).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field
3. Reviewer's report
Ryan Lennon

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The fundamental flaw in the analysis is the choice of endpoints. The primary endpoint ought to be harder than "further treatment" given that the purpose of the analysis is to estimate the effect of non-randomized treatment with tranexamic acid (TA). It is quite possible, perhaps very likely, that in a hospital where TA is clearly believed to be beneficial, physicians were more aggressive (maybe subconsciously so) in responding to blood loss in patients who had not received TA. Tables 8 and 9 could be consistent with such a hypothesis. If the amount of blood loss were higher in the NTA group, but physicians were more likely to transfuse NTA patients with little blood loss, this would pull the distribution of units transfused downward in the NTA group. Table 9 consists of patients who did not return to theatre. One may consider these patients to be less aggressively treated and these patients had similar rates of transfusion. This does not mean that the entire estimated benefit of TA is necessarily due to this bias, but much of it may be. The estimated effect is really a combination of clinical efficacy and physician response. Given the authors concern that large-scale clinical trials with TA are unlikely to occur, it is important to estimate TA's clinical effect with as little bias as possible. The authors ought to employ blood loss as their primary endpoint. If the authors choose to retain the current endpoints (in addition to blood loss) they should comment on the selection bias for these soft endpoints in the limitations section. The authors' argument in response to reviewers that including blood loss may "distract a reader from ... what matters" is nonsense. If I were a patient, blood loss would certainly matter. Return to theatre and transfusion are merely responses to that blood loss. It is unfortunate that other hard endpoints such as mortality are not available.

We agree with this this reviewer that clinicians may be affected by the administration of tranexamic acid in their decision to transfuse or take back to theatre. While this is most unlikely to have happened in our study for many reasons, such as the fact that the information regarding the administration of tranexamic acid is not readily available to the ones prescribing transfusion or deciding take back to theatre; the strict use (and adherence) to our institutional guidelines; the demonstration in our analysis, and finally the difference in blood loss between the group (now reported on your request and corroborating our findings).

We have added the following in the discussion to address these points:

In the absence of randomisation, a subjective effect cannot entirely be discarded by which physicians may be unconsciously biased towards administering less transfusion to those patients having received tranexamic acid. However, we believe that this is unlikely to have tainted our primary end-points as (1) adherence to the institutional protocol was similar for both patients receiving or not tranexamic acid (In the TA group 1207 (78%) of transfused patients were transfused according to guidelines compared with 319 (75%) in the NTA group, the difference is non-significant (p=0.124, Chi-squared test)); (2) a significant difference in the amount of blood loss measured in those patients treated with tranexamic acid when compared

The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery. Comments to reviewers - 6
with those who were not; (3) the effect of tranexamic acid being independent of the lead surgeon or anaesthetist involved in the case in our multivariate analysis; (4) the fact that the size of the institution and clinical pathways usually prevent clinicians prescribing postoperative transfusion and involved in the decision to take back to be aware if the administration of tranexamic acid effectively took place (as all patients should have received it).

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In Table 2, report actual p-values instead of "ns" or "< 0.05". There is no need to blunt that information. In Table 2, the test for comparing "Priority" should be accomplished by either a single chi-square test or a single rank sum test with the categories scored as 1=elective, 2=urgent, 3=emergency. The current three separate tests are highly correlated and possibly misleading.

We have modified table 2 accordingly, and have included p-values – note that only a single chi-squared test was performed (the same p-value or ns was copied from line to line by mistake).

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Discretionary Revisions (which the author can choose to ignore)

1. The choice between multivariable regression models and propensity score approach for covariate adjustment is often determined by analyst preference. Both have the same limitations in that neither can account for unmeasured covariates (outside of those covariates' associations with the measured covariates). If one has the variables to produce a regression model, they can also use a propensity score approach. Advantages of the propensity score approach are: 1) allows the analyst to consider more parameters (especially interactions) than the multivariable model may be able to numerically support; 2) when grouping the patients into propensity score-based strata and estimating the effect within those strata, it may become clear that the treatment has stronger effects in different groups of patients, e.g. a larger effect in higher risk patients; 3) the analyst does not have to build/describe separate models for each endpoint; 4) the model for the propensity score often indicates the amount of selection bias to be overcome via the c-statistic. With regards to this last point, while a higher c-statistic means that the propensity score discriminates well between the two groups, it also means that the two groups were very different to begin with and that unmeasured covariates may be similarly unbalanced. The advantages of the multiple regression model is that 1) it is easier to conduct; 2) it produces estimates of the associations between the covariates and the endpoint. The paper would be stronger with a propensity score approach, but this is not necessary. However, since the main focus of the paper is estimating the effect of TA, and not building models for the endpoints, the authors should allow all relevant covariates in the model, regardless of statistical significance. They should also allow for non-linear associations between the continuous covariates and the endpoints.

We thank the reviewer for this explanation.

The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery. Comments to reviewers - 7
2. Table 2 - The summary of EuroScore does not indicate which group has the higher scores in general. Consider reporting additional statistics to make this clearer, e.g. mean, 95th percentile, etc.

We have added a comment in the legend to the table to indicate the difference of Euroscore between the 2 groups.

Baseline characteristics of the patient cohort analysed. Patients who were in the tranexamic acid group were older, had a higher EuroSCORE (mean (SD) 4.61 (3.12) compared to 4.36 (3.13) in the NTA group) and higher proportion of them underwent combined procedures. Despite this, the rates of transfusion of RBC, FFP, all blood products and the rate of return to theatre for bleeding were lower for patients in this group. (TA - tranexamic acid, NTA - no tranexamic acid, SD – Standard Deviation, CABG – coronary artery bypass grafting, Valve – single valve repair or replacement, combined – coronary artery bypass grafting and single valve surgery, BMI – body mass index, RBC – red blood cells, FFP – fresh frozen plasma, ICU – intensive care unit, n – number, IQR – inter quartile range)